10/726 148

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=> d his

     (FILE 'HOME' ENTERED AT 14:43:00 ON 07 JUL 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:43:25 ON 07 JUL 2004
L1         18018 S "ADAM"
L2             2 S "A DISTINTEGRIN AND METALLOPROTEASE"
L3             2 DUP REM L2 (0 DUPLICATES REMOVED)
L4        416281 S PROTEASE OR DINITEGRIN
L5        420704 S PROTEASE OR DISINTEGRIN
L6          1933 S L1 AND L5
L7           990 S HUMAN AND L6
L8       6594644 S CLON? OR EXPRESS? OR RECOMBINANT
L9           751 S L7 AND L8
L10            0 S PROTEOIGLYCAN
L11        91811 S PROTEOGLYCAN
L12           28 S L9 AND L11
L13           14 DUP REM L12 (14 DUPLICATES REMOVED)
                 E YOSHIMURA K/AU
L14         3665 S E3
                 E HIKICHI Y/AU
L15          273 S E3
                 E NISHIMURA A/AU
L16         1666 S E3
L17         5594 S L14 OR L15 OR L16
L18            0 S L1 AND L17
L19           82 S L5 AND L17
L20           37 DUP REM L19 (45 DUPLICATES REMOVED)
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 NEWS  3  May 12   EXTEND option available in structure searching
 NEWS  4  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS  5  May 27   New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
 NEWS  6  May 27   CAplus super roles and document types searchable in REGISTRY
 NEWS  7  Jun 22   STN Patent Forums to be held July 19-22, 2004
 NEWS  8  Jun 28   Additional enzyme-catalyzed reactions added to CASREACT
 NEWS  9  Jun 28   ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG,
                   and WATER from CSA now available on STN(R)

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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FILE 'HOME' ENTERED AT 14:43:00 ON 07 JUL 2004

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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FILE 'LIFESCI' ENTERED AT 14:43:25 ON 07 JUL 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

=> s "ADAM"
L1 18018 "ADAM"

=> s "a distintegrin and metalloprotease"
L2 2 "A DISTINTEGRIN AND METALLOPROTEASE"

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 2 DUP REM L2 (0 DUPLICATES REMOVED)

=> d 1-2 ibib ab

L3 ANSWER 1 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003255058 EMBASE
TITLE: The Notch ligand Delta1 is sequentially cleaved by an ADAM protease and γ-secretase.
AUTHOR: Six E.; Ndiaye D.; Laabi Y.; Brou C.; Gupta-Rossi N.; Israel A.; Logeat F.
CORPORATE SOURCE: A. Israel, U. du Developpement des Lymphocytes, Ctr. Natl. de la Rech. Scientifique, Institut Pasteur, 25 Rue du Docteur Roux, 75724 Paris Cedex 15, France. aisrael@pasteur.fr
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (24 Jun 2003) 100/13 (7638-7643). Refs: 39
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Notch signaling is involved in numerous cell fate decisions in invertebrates and vertebrates, The Notch receptor is a type I transmembrane (TM) protein that undergoes two proteolytic steps after ligand binding, first by an ADAM (**a distintegrin** and **metalloprotease**) in the extracellular region, followed by γ-secretase-mediated cleavage inside the TM domain. We demonstrate here that the murine ligand Delta1 (DII1) undergoes the same sequence of cleavages, in an apparently signal-independent manner, Identification of the ADAM-mediated shedding site localized 10 aa N-terminal to the TM domain has enabled us to generate a noncleavable mutant. Kuzbanian/ADAM10 is involved in this processing event, but other proteases can probably substitute for it, We then show that DII1 is part of a high-molecular-weight complex containing presenilin1 and undergoes further

cleavage by a γ-secretase-like activity, therefore releasing the intracellular domain that localizes in part to the nucleus, Using the shedding-resistant mutant, we demonstrate that this γ-secretase cleavage depends on prior ectodomain shedding, Therefore DII1 is a substrate for regulated intramembrane proteolysis, and its intracellular region possibly fulfills a specific function in the nucleus.

L3 ANSWER 2 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003445485 EMBASE
TITLE: Shear Stress and von Willebrand Factor in Health and Disease.
AUTHOR: Tsai H.-M.
CORPORATE SOURCE: Dr. H.-M. Tsai, Division of Hematology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, United States. htsai@montefiore.org
SOURCE: Seminars in Thrombosis and Hemostasis, (2003) 29/5 (479-488).
Refs: 45
ISSN: 0094-6176 CODEN: STHMBV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Blood flow in the circulation creates shear stress that affects cell functions and cell-cell interactions. Recent studies reveal that shear stress is also critical in the homeostasis of the plasma glycoprotein von Willebrand factor (vWF). Because of its large molecular size, vWF has a flexible conformation that is uniquely responsive to shear stress. Exposure to shear stress causes conformational unfolding of vWF, enhancing its susceptibility to cleavage by a plasma zinc metalloprotease (a disintegrin and metalloprotease with thrombospondin type 1 motif [ADAMTS13]). In the absence of ADAMTS13, shear stress increases the capacity of vWF to support platelet aggregation. In normal individuals, a balance between endothelial secretion of an ultralarge form of vWF and intravascular proteolysis determines the size distribution of vWF multimers that seems to be optimum for hemostasis without imposing the risk of unwarranted platelet aggregation. In type 2A (group 2) von Willebrand disease, the mutant vWF is excessively susceptible to cleavage by ADAMTS13, resulting in a decrease of large vWF multimers and bleeding diathesis. In patients with aortic stenosis or the hemolytic-uremic syndrome, abnormally high levels of shear stress across the stenotic valve or in the microcirculation inflicted with thrombosis may promote cleavage of vWF by ADAMTS13, contributing to the loss of large multimers commonly observed among these patients. Conversely, a deficiency in ADAMTS13 because of genetic mutations or autoimmune inhibitors causes vWF- and platelet-rich microvascular thrombosis characteristic of thrombotic thrombocytopenic purpura.

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     (FILE 'HOME' ENTERED AT 14:43:00 ON 07 JUL 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:43:25 ON 07 JUL 2004
L1         18018 S "ADAM"
L2             2 S "A DISTINTEGRIN AND METALLOPROTEASE"
L3             2 DUP REM L2 (0 DUPLICATES REMOVED)

=> s protease or dinitegrin
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L4      416281 PROTEASE OR DINITEGRIN

=> s protease or disintegrin
L5      420704 PROTEASE OR DISINTEGRIN

=> s l1 and l5
L6        1933 L1 AND L5

=> s human and l6
L7         990 HUMAN AND L6

=> s clon? or express? or recombinant
   5 FILES SEARCHED...
L8     6594644 CLON? OR EXPRESS? OR RECOMBINANT

=> s l7 and l8
L9         751 L7 AND L8

=> s proteoiglycan
L10          0 PROTEOIGLYCAN

=> s proteoglycan
L11      91811 PROTEOGLYCAN

=> s l9 and l11
L12         28 L9 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13          14 DUP REM L12 (14 DUPLICATES REMOVED)

=> d 1-14 ibib ab

L13  ANSWER 1 OF 14  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER:    2004:355817  SCISEARCH
THE GENUINE ARTICLE: 810JX
TITLE:               Dysregulated expression of adamalysin-
                     thrombospondin genes in human breast carcinoma
AUTHOR:              Porter S; Scott S D; Sassoon E M; Williams M R; Jones J L;
                     Girling A C; Ball R Y; Edwards D R (Reprint)
CORPORATE SOURCE:    Univ E Anglia, Sch Biol Sci, Norwich NR4 7TJ, Norfolk,
                     England (Reprint); Leicester Royal Infirm, Dept Pathol,
                     Leicester LE2 7LX, Leics, England; Norwich Univ Hosp NHS
                     Trust, Norwich, Norfolk, England; Dept Gen Surg, Norfolk,
                     England; Dept Plast Surg, Norfolk, England; Dept
                     Histopathol, Norfolk, England
COUNTRY OF AUTHOR:   England
SOURCE:              CLINICAL CANCER RESEARCH, (1 APR 2004) Vol. 10, No. 7, pp.
                     2429-2440.
                     Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST,
                     17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
                     ISSN: 1078-0432.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     49
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       The adamalysin-thrombospondin (ADAMTS) proteinases are a relatively
     newly described branch of the metzincin family that contain
     metalloproteinase, disintegrin, and thrombospondin motifs. They
     have been implicated in various cellular events, including cleavage of
     proteoglycans, extracellular matrix degradation, inhibition of
     angiogenesis, gonadal development, and organogenesis. However, in many
     cases, their normal physiological roles and their potential for
     dysregulation in malignancy remain to be established. The
```

expression profile of ADAMTS1-20 in **human** breast carcinoma was undertaken by real-time PCR using RNA isolated from malignant tumors, nonneoplastic mammary tissue, and breast cancer cell lines to identify altered regulation that may have potential pathogenetic and prognostic significance. Our studies show that seven of the ADAMTS genes (ADAMTS1, 3, 5, 8, 9, 10, and 18) are consistently down-regulated in breast carcinomas with respect to nonneoplastic mammary tissue, irrespective of the heterogeneity of the samples and the tumor type or grade (Mann-Whitney U test, $P < 0.0001$ for each gene). Conversely, ADAMTS4, 6, 14, and 20 are consistently up-regulated in breast carcinomas ($P = 0.005$, $P < 0.0001$, $P = 0.003$, and $P = 0.001$, respectively). ADAMTS2, 7, 12, 13, 15, 16, 17, and 19 show no significant difference between the sample types. ADAMTS1, 2, 7, 8, 10, and 12 are **expressed** predominantly in stromal fibroblasts. ADAMTS3, 4, 5, 6, 9, and 13-20 inclusive are **expressed** predominantly in myoepithelial cells; all appear to be relatively poorly **expressed** in luminal epithelial cells. ADAMTS15 has emerged as being an independent predictor of survival, with RNA **expression** levels significantly lower ($P = 0.007$) in grade 3 breast carcinoma compared with grade 1 and 2 breast carcinoma.

L13 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313

PRIORITY APPLN. INFO.:
JP 2001-73183 A 20010314
JP 2001-74993 A 20010315
JP 2001-102519 A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose **expression** is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L13 ANSWER 3 OF 14 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:710786 SCISEARCH
THE GENUINE ARTICLE: 467RY
TITLE: **ADAM**-10 protein is present in **human** articular cartilage primarily in the membrane-bound form and is upregulated in osteoarthritis and in response to 1L-1 alpha in bovine nasal cartilage

AUTHOR: Chubinskaya S (Reprint); Mikhail R; Deutsch A; Tindal M H
CORPORATE SOURCE: Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, 1653 W Congress Pkwy, Chicago, IL 60612 USA (Reprint); Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, Chicago, IL 60612 USA; Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Rheumatol Sect, Chicago, IL 60612 USA; Procter & Gamble Pharmaceut Inc, Hlth Care Res Ctr, Mason, OH USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF HISTOCHEMISTRY & CYTOCHEMISTRY, (SEP 2001) Vol. 49, No. 9, pp. 1165-1176.
Publisher: HISTOCHEMICAL SOC INC, UNIV WASHINGTON, DEPT BIOSTRUCTURE, BOX 357420, SEATTLE, WA 98195 USA.
ISSN: 0022-1554.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of our study was to determine the tissue distribution and localization of **ADAM**-10 protein in **human** and bovine cartilage and the changes it undergoes with cartilage degeneration seen in osteoarthritis (OA) and under the influence of interleukin-1 (IL-1). **Human** normal and OA articular cartilage and bovine nasal cartilage cultured in the presence of IL-1 alpha were processed for histology and immunohistochemistry. **ADAM**-10 protein was extracted from **human** cartilage and analyzed by Western blotting using anti-**ADAM**-10 antibodies. Fluor 5 Image analyzer and Quantity One software program were applied to quantify the total amount of **ADAM** -10. **ADAM**-10 protein was detected in both **human** and bovine cartilage. The strongest immunostaining was found in the cytoplasm and/or cell membranes of the superficial and upper middle layer of normal adult **human** cartilage, in the clusters and fibrillated areas of OA cartilage, and in IL-1 alpha -stimulated bovine nasal cartilage. The distribution of **ADAM**-10 protein in bovine nasal cartilage was dependent on the length of exposure to IL-1 alpha and corresponded to the areas of **proteoglycan** depletion. By Western blotting analysis of **human** cartilage, **ADAM**-10 was primarily detected in the membrane-enriched fraction and its levels were increased in degenerated and OA cartilage compared to normal cartilage. The results of this study suggest that **ADAM**-10 might be an important factor associated with cartilage degenerative processes.

L13 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001477558 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11520168
TITLE: The role of **ADAM**-TS4 (aggrecanase-1) and **ADAM**-TS5 (aggrecanase-2) in a model of cartilage degradation.
COMMENT: Erratum in: Osteoarthritis Cartilage 2002 Jan;10(1):82
AUTHOR: Tortorella M D; Malfait A M; Deccico C; Arner E
CORPORATE SOURCE: DuPont Pharmaceuticals Company, Wilmington, DE 19880-0400, USA.. micky.d.tortorella@pharmacia.com
SOURCE: Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, (2001 Aug) 9 (6) 539-52.
Journal code: 9305697. ISSN: 1063-4584.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20020313
Entered Medline: 20011004

AB INTRODUCTION: Cleavage of aggrecan between residues Glu(373)-Ala(374),

which is believed to be a key event in aggrecan destruction in arthritic diseases, has been attributed to an enzymatic activity, aggrecanase. Two cartilage aggrecanases have been identified, aggrecanase-1 (**ADAM** -TS4) and aggrecanase-2 (**ADAM**-TS5) and both enzymes have been shown very efficiently to cleave soluble aggrecan at the Glu(373)-Ala(374) site. OBJECTIVE: To determine whether **ADAM**-TS4 and/or **ADAM**-TS5 are the aggrecanases responsible for aggrecan catabolism following interleukin-1 (IL-1) and tumor necrosis factor (TNF) treatment of bovine articular cartilage. RESULTS: (1) IL-1- and TNF-stimulated release of aggrecan was associated with cleavage of aggrecan within the C-terminus at the **ADAM**-TS4 and **ADAM**-TS5-sensitive sites, Glu(1480)-Gly(1481), Glu(1667)-Gly(1668), and Glu(1871)-Leu(1872). (2) The order of cleavage following IL-1 stimulation of cartilage explants was the same as when soluble aggrecan is digested with **recombinant human ADAM**-TS4 and **ADAM**-TS5. (3) Both constitutive and stimulated cleavage of aggrecan at the **ADAM**-TS4 and **ADAM**-TS5-sensitive sites in cartilage was blocked by a general metalloproteinase inhibitor but not by a MMP-specific inhibitor, and this inhibition correlated with inhibition of aggrecan release from cartilage. (4) PCR and Western blot analysis indicated that both **ADAM**-TS **proteases** are **expressed** in cartilage explants; **ADAM**-TS5 is constitutively **expressed** whereas **ADAM**-TS4 is induced following IL-1 and TNF treatment. (5) Immunodepletion of both **ADAM**-TS4 and **ADAM**-TS5 from bovine articular cartilage cultures following IL-1 stimulation resulted in a 90% reduction of aggrecanase activity in the culture medium.

L13 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:175926 HCAPLUS
DOCUMENT NUMBER: 132:218866
TITLE: **Cloning** of cDNA for novel **human** **ADAM** family protein and its clinical use
INVENTOR(S): Yoshimura, Koji; Hikichi, Yuichi; Nishimura, Atsushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014227	A1	20000316	WO 1999-JP4766	19990902
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2341327	AA	20000316	CA 1999-2341327	19990902
AU 9954479	A1	20000327	AU 1999-54479	19990902
JP 2000139480	A2	20000523	JP 1999-248436	19990902
EP 1111047	A2	20010627	EP 1999-940629	19990902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6680189	B1	20040120	US 2001-786256	20010510

PRIORITY APPLN. INFO.: JP 1998-250115 A 19980903
WO 1999-JP4766 W 19990902

AB The cDNA encoding a novel protein belonging to the **ADAM** (a **disintegrin** and metalloprotease) family are isolated from

human and its amino acid sequence deduced. The amino acid sequences deduced from **clone** pTB2052 and **clone** pTB2053 are comprised of 775 and 540 residues, resp. Methods of screening the agonists or the antagonists of **protease** or extracellular matrix-degrading enzyme by using the protein; prophylactics or therapeutics containing the protein for disk hernia, sciatic neuralgia, glomerulonephritis nephritis, diabetic nephropathy, hepatic fibrosis, lung fibrosis, osteopetrosis; methods of screening **proteoglycan** -degrading enzymes and their agonists or antagonists; and transgenic animals **expressing** the gene are claimed.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2000270266 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10809781
TITLE: Role of Src kinases in the **ADAM**-mediated release of L1 adhesion molecule from **human** tumor cells.
AUTHOR: Gutwein P; Oleszewski M; Mechtersheimer S; Agmon-Levin N; Krauss K; Altevogt P
CORPORATE SOURCE: Tumor Immunology Programme, 0710, German Cancer Research Center, D-69120 Heidelberg, Germany.
SOURCE: Journal of biological chemistry, (2000 May 19) 275 (20) 15490-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB The ectodomain of certain transmembrane molecules can be released by proteolysis, and the solubilized antigens often exert important biological functions. We demonstrated before that the L1 adhesion molecule is shed from the cell surface. Here we show that L1 release in AR breast carcinoma cells is mediated by a member of the **disintegrin** metalloproteinase (**ADAM**) family of proteinases. Up-regulation of L1 shedding by phorbol ester or pervanadate involved distinct mechanisms. Pervanadate induced shedding and rounding-up of cells from the substrate, which was blocked by the Src kinase inhibitor PP2. Tyr phosphorylation of the L1 cytoplasmic tail and the Src kinase Fyn was observed following pervanadate treatment. Up-regulation of L1 release and activation of Fyn occurred also when cells were detached by EDTA suggesting that the regulation of L1 shedding by this pathway was linked to cell morphology and adhesion. The phorbol 12-myristate 13-acetate-induced shedding was inhibited by the protein kinase C inhibitor bisindolylmaleimide I and by PD98059, a specific inhibitor of the mitogen-activated protein kinase pathway. Soluble L1 binds to the **proteoglycan** neurocan and in bound form could support integrin-mediated cell adhesion and migration. We propose that the release of cell-associated adhesion molecules such as L1 may be relevant to promote cell migration.

L13 ANSWER 7 OF 14 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000293210 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10831617
TITLE: The cysteine-rich domain of **human ADAM** 12 supports cell adhesion through syndecans and triggers signaling events that lead to beta1 integrin-dependent cell spreading.
COMMENT: Comment in: J Cell Biol. 2000 May 29;149(5):995-8. PubMed ID: 10831602

AUTHOR: Iba K; Albrechtsen R; Gilpin B; Frohlich C; Loechel F; Zolkiewska A; Ishiguro K; Kojima T; Liu W; Langford J K; Sanderson R D; Brakebusch C; Fassler R; Wewer U M
CORPORATE SOURCE: The Institute of Molecular Pathology, University of Copenhagen, 2100 Copenhagen, Denmark.
CONTRACT NUMBER: CA68494 (NCI)
SOURCE: Journal of cell biology, (2000 May 29) 149 (5) 1143-56. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20021227
Entered Medline: 20000706

AB The **ADAMs** (a **disintegrin** and metalloprotease) family of proteins is involved in a variety of cellular interactions, including cell adhesion and ecto- domain shedding. Here we show that **ADAM** 12 binds to cell surface syndecans. Three forms of **recombinant ADAM** 12 were used in these experiments: the cys-teine-rich domain made in Escherichia coli (rADAM 12-cys), the **disintegrin**-like and cysteine-rich domain made in insect cells (rADAM 12-DC), and full-length **human ADAM** 12-S tagged with green fluorescent protein made in mammalian cells (rADAM 12-GFP). Mesenchymal cells specifically and in a dose-dependent manner attach to **ADAM** 12 via members of the syndecan family. After binding to syndecans, mesenchymal cells spread and form focal adhesions and actin stress fibers. Integrin beta1 was responsible for cell spreading because function-blocking monoclonal antibodies completely inhibited cell spreading, and chondroblasts lacking beta1 integrin attached but did not spread. These data suggest that mesenchymal cells use syndecans as the initial receptor for the **ADAM** 12 cysteine-rich domain-mediated cell adhesion, and then the beta1 integrin to induce cell spreading. Interestingly, carcinoma cells attached but did not spread on **ADAM** 12. However, spreading could be efficiently induced by the addition of either 1 mM Mn(2+) or the beta1 integrin-activating monoclonal antibody 12G10, suggesting that in these carcinoma cells, the **ADAM** 12-syndecan complex fails to modulate the function of beta1 integrin.

L13 ANSWER 8 OF 14 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000427936 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10936055
TITLE: ADAMTS9, a novel member of the **ADAM**-TS/ metallospondin gene family.
AUTHOR: Clark M E; Kelner G S; Turbeville L A; Boyer A; Arden K C; Maki R A
CORPORATE SOURCE: Department of Molecular Biology, Neurocrine Biosciences Inc., San Diego, California 92121, USA.. mclark@neurocrine.com
SOURCE: Genomics, (2000 Aug 1) 67 (3) 343-50. Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000922
Last Updated on STN: 20000922
Entered Medline: 20000914

AB **ADAM**-TS/metallospondin genes encode a new family of proteins with structural homology to the **ADAM** metalloprotease-**disintegrin** family. However, unlike other **ADAMs**, these proteins contain thrombospondin type 1 (TSP1) repeats at the

carboxy-terminal end and are secreted proteins instead of being membrane bound. Members of the **ADAM**-TS family have been implicated in the cleavage of **proteoglycans**, the control of organ shape during development, and the inhibition of angiogenesis. We have **cloned** a new member of the **ADAM**-TS/metallospondin family designated here as ADAMTS9. This protein has a metalloprotease domain, a **disintegrin**-like domain, one internal TSP1 motif, and three carboxy-terminal TSP1-like submotifs. In contrast to other **ADAM** -TS family members, ADAMTS9 is **expressed** in all fetal tissues examined as well as some adult tissues. Using FISH and radiation hybrid analysis, we have localized ADAMTS9 to chromosome 3p14.2-p14.3, an area known to be lost in hereditary renal tumors.

L13 ANSWER 9 OF 14 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:927231 SCISEARCH
THE GENUINE ARTICLE: 379NL
TITLE: Cellular localization of the **disintegrin** CRII-7/rMDC15 mRNA in rat PNS and CNS and regulated **expression** in postnatal development and after nerve injury
AUTHOR: Bosse F (Reprint); Petzold G; GreinerPetter R; Pippirs U; Gillen C; Muller H W
CORPORATE SOURCE: UNIV DUSSELDORF, DEPT NEUROL, MOL NEUROBIOL LAB, MOORENSTR 5, D-40225 DUSSELDORF, GERMANY (Reprint)
COUNTRY OF AUTHOR: GERMANY
SOURCE: GLIA, (DEC 2000) Vol. 32, No. 3, pp. 313-327.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0894-1491.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 61

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Disintegrins** perform putative functions in cell adhesion, signaling and fusion. We have isolated a 2815-bp rat cDNA (CRII-7) representing a transcript that is differentially **expressed** during sciatic nerve regeneration. Nucleotide sequence comparison indicates that CRII-7 is the rat homologue to the recently **cloned** cDNAs MDC15 (**ADAM** 15) and metargidin (hMDC15) of mouse and **human**, respectively. The CRII-7 cDNA (rMDC15) encodes a membrane-anchored glycoprotein of approximately 85 kDa containing a **disintegrin** and a metalloprotease domain. Cellular metalloprotease **disintegrins** are a family of proteins (**ADAMs** or MDC proteins) with important roles, e.g., in cell-cell interactions during fertilization, muscle and nerve development, or tumor necrosis factor-or (TNF-cw) cleavage. Northern blot analysis demonstrated a predominant **expression** of CRII-7/rMDC15 in the nervous system (PNS and CNS) and lung. Analysis of the CRII-7/rMDC15 transcript levels following peripheral nerve lesions demonstrated regulated mRNA **expression** during Wallerian degeneration and nerve regeneration. The steady-state levels of CRII-7/rMDC15 transcripts markedly increased within the first day after lesion and then steadily decreased for at least 4 weeks. CRII-7/rMDC15 mRNA **expression** was further examined during postnatal development and maturation of rat sciatic nerve and brain, as well as in cultured Schwann cells, meningeal fibroblasts, and astrocytes. In situ hybridization on paraffin sections showed the cellular localization of CRII-7/rMDC15 mRNA in Schwann cells and endothelial cells of peripheral nerve and in various neuronal populations in brain and spinal cord. (C) 2000 Wiley-Liss, Inc.

L13 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:428698 HCAPLUS

DOCUMENT NUMBER: 134:112014
TITLE: New metalloproteinase family, ADAMTS
AUTHOR(S): Kuno, Kouji
CORPORATE SOURCE: Cancer Res. Inst., Kanazawa Univ., Japan
SOURCE: Immunology Frontier (2000), 10(3), 159-166
CODEN: IMFREG; ISSN: 0917-0774
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 15 refs. on the structure and organ distribution of the ADAMTS family of metalloproteinases. **ADAM** (a **disintegrin** and metalloproteinase) family are the membranous **protease** participating in shedding of various mols.; ADAM17 is the tumor necrosis factor α converting enzyme (TACE). ADAMTS (**ADAM** family gene with thrombospondin motif) family are secretory **proteases** with thrombospondin (TSP) type 1 motif. ADAMTS-1 binds the extracellular matrix (ECM) by 3 TSP type 1 motives and spacer regions. ADAMTS-1 is **expressed** in various organs, and plays important role in formation and function of renal pelvis tissue. Anomaly in type I procollagen N-**protease** (pNP1, ADAMTS-2) causes disorder in dermal tissue in **human** Ehlers-Danlos syndrome type VIIC. Aggricase in ADAMTS family participates in degradation of cartilage **proteoglycan** in chronic rheumatoid arthritis and osteoarthritis, and it may be the therapeutic target.

L13 ANSWER 11 OF 14 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999263385 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10329602
TITLE: Cysteine-rich domain of **human ADAM** 12 (meltrin alpha) supports tumor cell adhesion.
AUTHOR: Iba K; Albrechtsen R; Gilpin B J; Loechel F; Wewer U M
CORPORATE SOURCE: Institute of Molecular Pathology, University of Copenhagen, Copenhagen, Denmark.
SOURCE: American journal of pathology, (1999 May) 154 (5) 1489-501. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 20030128
Entered Medline: 19990603

AB The **ADAMs** (A **disintegrin** and metalloprotease) comprise a family of membrane-anchored cell surface proteins with a putative role in cell-cell and/or cell-matrix interactions. By immunostaining, **ADAM** 12 (meltrin alpha) was up-regulated in several **human** carcinomas and could be detected along the tumor cell membranes. Because of this intriguing staining pattern, we investigated whether **human ADAM** 12 supports tumor cell adhesion. Using an in vitro assay using **recombinant** polypeptides **expressed** in Escherichia coli, we examined the ability of individual domains of **human ADAM** 12 and **ADAM** 15 to support tumor cell adhesion. We found that the **disintegrin**-like domain of **human ADAM** 15 supported adhesion of alphavbeta3-**expressing** A375 melanoma cells. In the case of **human ADAM** 12, however, **recombinant** polypeptides of the cysteine-rich domain but not the **disintegrin**-like domain supported cell adhesion of a panel of carcinoma cell lines. On attachment to **recombinant** polypeptides from the cysteine-rich domain of **human ADAM** 12, most tumor cell lines, such as MDA-MB-231 breast carcinoma cells, were rounded and associated with numerous actin-containing filopodia and used a cell surface heparan sulfate **proteoglycan** to attach. Finally, we demonstrated that authentic

full-length **human ADAM** 12 could bind to heparin Sepharose. Together these results suggest a novel role of the cysteine-rich domain of **ADAM** 12 -- that of supporting tumor cell adhesion.

L13 ANSWER 12 OF 14 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:549367 SCISEARCH
THE GENUINE ARTICLE: 215CV
TITLE: Mechanisms of **proteoglycan** metabolism that lead to cartilage destruction in the pathogenesis of arthritis
AUTHOR: Caterson B (Reprint); Flannery C R; Hughes C E; Little C B
CORPORATE SOURCE: UNIV WALES, CARDIFF SCH BIOSCI, CONNECT TISSUE BIOL LABS, MUSEUM AVE, BOX 911, CARDIFF CF1 EUS, S GLAM, WALES (Reprint); CARDIFF UNIV, CARDIFF SCH BIOSCI, CONNECT TISSUE BIOL LABS, CARDIFF, S GLAM, WALES
COUNTRY OF AUTHOR: WALES
SOURCE: DRUGS OF TODAY, (APR-MAY 1999) Vol. 35, No. 4-5, pp. 397-402.
Publisher: PROUS SCIENCE, SA, PO BOX 540, PROVENZA 388, 08025 BARCELONA, SPAIN.
ISSN: 0025-7656.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 16

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The mechanisms and agents involved in cartilage matrix destruction are poorly understood and at present there are no means of therapeutic intervention that halt or slow the degradative processes that result in tissue loss, joint space narrowing and the eventual need for surgery with total joint replacement. In recent years our laboratory has pioneered the development and use of monoclonal antibody (MAb) technologies for the study of changes in cartilage matrix metabolism in health and disease. In this chapter we have summarized results coming from our recent studies examining the mechanisms of cartilage **proteoglycan** (aggrecan) catabolism that precedes cartilage destruction in arthritis. This research has used two approaches. The first is our access to a panel of MAbs that recognize both constitutive structural epitopes and catabolic neoepitopes on cartilage **proteoglycan** metabolites. These antibodies have allowed us to determine whether the unknown proteolytic agent 'aggrecanase' or known matrix metalloproteinases (MMPs) are involved in the increased aggrecan catabolism that is observed in arthritis. Secondly, we have used reverse transcription-polymerase chain reaction (RT-PCR) techniques to profile the **expression** of members of the MMP family or **ADAMs** (A **disintegrin** and metalloproteinase) that are potentially involved in this degenerative process. Collectively these investigations have established that aggrecanase is the major proteolytic activity responsible for aggrecan loss in the early stages that lead to cartilage degradation in arthritis. In addition, our studies have allowed us to determine many important biochemical properties of aggrecanase without knowing the identity of the enzyme. Our data also calls into question the role that MMPs may play in the early stages of cartilage destruction that lead to surface fibrilation. However, MMPs may be involved in later stages where collagen degradation is prevalent. The role that **ADAMs** play is still unknown, although they are postulated to play an important role in shedding or activation of different classes of matrix **proteases**. Furthermore, we have observed changes in the patterns of cartilage **expression** in fresh tissue and model culture systems. This work has indicated clearly that there are several different classes of enzyme that can be targeted for innovative therapies which could slow or halt cartilage destruction in arthritis.

L13 ANSWER 13 OF 14 EMBASE

on STN DUPLICATE 5
ACCESSION NUMBER: 1999263307 EMBASE
TITLE: **Expression** of ADAMTS homologues in articular cartilage.
AUTHOR: Flannery C.R.; Little C.B.; Hughes C.E.; Caterson B.
CORPORATE SOURCE: C.R. Flannery, Connective Tissue Biology Lab., Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF1 3US, United Kingdom. FlanneryCR@Cardiff.ac.uk
SOURCE: Biochemical and Biophysical Research Communications, (5 Jul 1999) 260/2 (318-322).
Refs: 22
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Articular chondrocytes possess the capacity to **express** a number of **ADAM** (A **Disintegrin** And Metalloproteinase) family members, thereby implicating a role for such proteins in the turnover of cartilage extracellular matrix molecules. Recently, the sequence for the **human** orthologue of an 'aggrecanase' isolated from bovine nasal cartilage has been elucidated, and the **recombinant** protein product shown to be capable of cleaving aggrecan specifically at the relevant peptide bonds which are hydrolyzed in situ during cartilage degradation. The sequence for the **human** 'aggrecanase' exhibits homology with that of murine ADAMTS-1, an **ADAM** with thrombospondin type I motifs. In the present study we have identified additional ADAMTS homologues and have examined their mRNA **expression** profiles in freshly excised **human** articular cartilage and in **human** cartilage explant cultures stimulated with IL-1, TNF-α, or retinoic acid, agents which enhance 'aggrecanase' activity in vitro. Significantly, cartilage exposed to retinoic acid showed a marked increase in the release of 'aggrecanase'-generated aggrecan catabolites with no concomitant increase in mRNA levels for any of the ADAMTS homologues investigated. These findings indicate that enhanced 'aggrecanase' activity, which may be attributed to known ADAMTS homologues, may be predominantly regulated by post-transcriptional mechanism(s), and may raise the possiblility for the existence of other as yet unidentified 'aggrecanase(s)'.

L13 ANSWER 14 OF 14 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999357011 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10429942
TITLE: Effects of culture conditions and exposure to catabolic stimulators (IL-1 and retinoic acid) on the **expression** of matrix metalloproteinases (MMPs) and **disintegrin** metalloproteinases (**ADAMs**) by articular cartilage chondrocytes.
AUTHOR: Flannery C R; Little C B; Caterson B; Hughes C E
CORPORATE SOURCE: Connective Tissue Biology Laboratories, Cardiff School of Biosciences, Cardiff University, Wales, UK.. flannerycr@cardiff.ac.uk
SOURCE: Matrix biology : journal of the International Society for Matrix Biology, (1999 Jun) 18 (3) 225-37.
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF069641; GENBANK-AF069642; GENBANK-AF069643; GENBANK-AF069644; GENBANK-AF069645; GENBANK-AF069646;

GENBANK-AF069647; GENBANK-AF069648; GENBANK-AF069649
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991026

AB The chondrocytes of articular cartilage synthesize a number of proteinases which are capable of degrading the component molecules of this specialized extracellular matrix. The use of class-specific proteinase inhibitors indicates that major activities responsible for catabolism of **proteoglycan** (aggrecan) and collagen are attributable to zinc-dependent metalloproteinases. In this study, we have compared the mRNA **expression** profiles of two matrix metalloproteinases (MMP-3 and MMP-13) and five **disintegrin**-metalloproteinases (**ADAM**-10, **ADAM**-9, **ADAM**-15, TNF-alpha-converting enzyme and decysin) by chondrocytes (**human**, porcine and bovine) from fresh cartilage and in cartilage explant cultures and isolated cells cultured in monolayer or in agarose gels. Such cultures were maintained in the presence or absence of interleukin-1 (IL-1) or all-trans-retinoic acid, two agents which promote cartilage matrix degradation in vitro. Whereas transcripts for all metalloproteinases examined were detected in chondrocytes from **human** osteoarthritic cartilage in monolayer cultures, mRNAs for **ADAM**-15 and decysin were not present in fresh osteoarthritic **human** cartilage or explant cultures. Similarly, **expression** of porcine and bovine metalloproteinase mRNAs varied with different culture conditions. Novel cDNA sequences obtained for porcine and bovine MMP-3 and MMP-13, porcine **ADAM** -10, porcine and bovine **ADAM**-9 and porcine TACE confirmed **expression** of mRNAs for these molecules by articular chondrocytes. Quantitative RT-PCR analysis was used to determine the effects of IL-1 and retinoic acid on metalloproteinase mRNA levels in **human** chondrocytes cultured in monolayer and in porcine chondrocytes cultured in agarose. For the MMPs, IL-1 treatment resulted in an approximately two to threefold increase in **human** and porcine MMP-3 and MMP-13 mRNAs, while retinoic acid treatment caused a statistically significant increase in **human** MMP-3 mRNA levels, but no significant change in transcript levels for porcine MMP-3 nor **human** or porcine MMP-13. The mRNA levels for **ADAM**-15 were elevated in **human** monolayer chondrocytes exposed to IL-1 or retinoic acid, while transcripts levels for TNF-alpha converting enzyme were increased in response to retinoic acid. In contrast, **ADAM**-9 mRNA levels were decreased in **human** monolayer chondrocytes exposed to IL-1 or retinoic acid. The results demonstrate that chondrocyte metalloproteinase **expression** can vary dependent on cell environment in situ and in vitro, and information on chondrocyte MMP and **ADAM** gene **expression** following cytokine (IL-1) or retinoid stimulation.

```
=> e yoshimura k/au
E1            1     YOSHIMURA JYUN YA/AU
E2            2     YOSHIMURA JYUNICHI/AU
E3         3665 --> YOSHIMURA K/AU
E4            2     YOSHIMURA K */AU
E5            2     YOSHIMURA K I/AU
E6            1     YOSHIMURA K O H/AU
E7            1     YOSHIMURA KAICHI/AU
E8            9     YOSHIMURA KAN/AU
E9            1     YOSHIMURA KANICHI/AU
E10          26     YOSHIMURA KANJI/AU
E11           1     YOSHIMURA KAORI/AU
E12           7     YOSHIMURA KAORU/AU

=> s e3
L14        3665 "YOSHIMURA K"/AU
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=> e hikichi y/au
E1            1     HIKICHI TOSHITAKA/AU
E2            1     HIKICHI TOSHIYA/AU
E3          273 --> HIKICHI Y/AU
E4           58     HIKICHI YASUFUMI/AU
E5          118     HIKICHI YASUO/AU
E6            1     HIKICHI YASUSHI/AU
E7           29     HIKICHI YOSHINAO/AU
E8           18     HIKICHI YUICHI/AU
E9            2     HIKICHI YUKA/AU
E10          17     HIKICHI YUKIKO/AU
E11           6     HIKICHI YUTAKA/AU
E12           1     HIKICJI KAZUMASA/AU

=> s e3
L15         273 "HIKICHI Y"/AU

=> e nishimura a/au
E1            1     NISHIMUR YOSHIAKI/AU
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E3         1666 --> NISHIMURA A/AU
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E5            1     NISHIMURA A H/AU
E6           30     NISHIMURA A L/AU
E7          100     NISHIMURA A M/AU
E8            1     NISHIMURA AGNES/AU
E9            4     NISHIMURA AGNES L/AU
E10           2     NISHIMURA AKANE M/AU
E11           7     NISHIMURA AKEMI/AU
E12           4     NISHIMURA AKI/AU

=> s e3
L16        1666 "NISHIMURA A"/AU

=> d his

     (FILE 'HOME' ENTERED AT 14:43:00 ON 07 JUL 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:43:25 ON 07 JUL 2004
L1         18018 S "ADAM"
L2             2 S "A DISTINTEGRIN AND METALLOPROTEASE"
L3             2 DUP REM L2 (0 DUPLICATES REMOVED)
L4        416281 S PROTEASE OR DINITEGRIN
L5        420704 S PROTEASE OR DISINTEGRIN
L6          1933 S L1 AND L5
L7           990 S HUMAN AND L6
L8       6594644 S CLON? OR EXPRESS? OR RECOMBINANT
L9           751 S L7 AND L8
L10            0 S PROTEOIGLYCAN
L11        91811 S PROTEOGLYCAN
L12           28 S L9 AND L11
L13           14 DUP REM L12 (14 DUPLICATES REMOVED)
                 E YOSHIMURA K/AU
L14         3665 S E3
                 E HIKICHI Y/AU
L15          273 S E3
                 E NISHIMURA A/AU
L16         1666 S E3

=> s l14 or l15 or l16
L17        5594 L14 OR L15 OR L16

=> s l1 and l17
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L18 0 L1 AND L17

=> s l5 and l17
L19 82 L5 AND L17

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20 37 DUP REM L19 (45 DUPLICATES REMOVED)

=> d 1-37 ibib ab

L20 ANSWER 1 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
ACCESSION NUMBER: 2004091607 EMBASE
TITLE: Evidence for HrpXo-Dependent Expression of Type II Secretory Proteins in Xanthomonas oryzae pv. oryzae.
AUTHOR: Furutani A.; Tsuge S.; Ohnishi K.; **Hikichi Y.**; Oku T.; Tsuno K.; Inoue Y.; Ochiai H.; Kaku H.; Kubo Y.
CORPORATE SOURCE: S. Tsuge, Laboratory of Plant Pathology, Graduate School of Agriculture, Kyoto Prefectural University, Kyoto 606-8522, Japan. s_tsuge@love.kpu.ac.jp
SOURCE: Journal of Bacteriology, (2004) 186/5 (1374-1380).
Refs: 41
ISSN: 0021-9193 CODEN: JOBAAY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Xanthomonas oryzae pv. oryzae is a causal agent of bacterial leaf blight of rice. Recently, an efficient hrp-inducing medium, XOM2, was established for this bacterium. In this medium, more than 10 proteins were secreted from the wild-type strain of X. oryzae pv. oryzae Many of these proteins disappeared or decreased in amount in culture on XOM2 when incubated with the strain that has a mutation in the hrp regulatory gene. Interestingly, the secretory protein profile of a mutant lacking a type III secretion system (TTSS), components of which are encoded by hrp genes, was similar to that of the wild-type strain except that a few proteins had disappeared. This finding suggests that many HrpXo-dependent secretory proteins are secreted via systems other than the TTSS. By isolating mutant strains lacking a type II secretion system, we examined this hypothesis. As expected, many of the HrpXo-dependent secretory proteins disappeared or decreased when the mutant was cultured in XOM2. By determining the N-terminal amino acid sequence, we identified one of the type II secretory proteins as a cysteine **protease** homolog, CysP2. Nucleotide sequence analysis revealed that cysP2 has an imperfect plant-inducible-promoter box, a consensus sequence which HrpXo regulons possess in the promoter region, and a deduced signal peptide sequence at the N terminus. By reverse transcription-PCR analysis and examination of the expression of CysP2 by using a plasmid harboring a cysP2::gus fusion gene, HrpXo-dependent expression of CysP2 was confirmed. Here, we reveal that the hrp regulatory gene hrpXo is also involved in the expression of not only hrp genes and type III secretory proteins but also some type II secretory proteins.

L20 ANSWER 2 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-15464 BIOTECHDS
TITLE: Screening promoters or inhibitors of proteoglycan decomposition as preventives for bone and joint diseases with use of cells expressing matrix metalloproteinase (MMP)-19 and membrane-type (MT)3-MMP, particularly for rheumatoid arthritis;
proteoglycan decomposition promoter and inhibitor for use in drug screening

AUTHOR: **YOSHIMURA K; HIKICHI Y**
PATENT ASSIGNEE: TAKEDA CHEM IND LTD
PATENT INFO: WO 2003029819 10 Apr 2003
APPLICATION INFO: WO 2002-JP9949 26 Sep 2002
PRIORITY INFO: JP 2001-303314 28 Sep 2001; JP 2001-303314 28 Sep 2001
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: WPI: 2003-372019 [35]
AB DERWENT ABSTRACT:

NOVELTY - Screening compounds or their salts promoting or inhibiting proteoglycan decomposition is by using a combination of a protein based on the sequence of (I) of 508 amino acids, and another protein with an amino acid sequence identical or substantially similar to that of (II) of 457 amino acids, its partial peptide, is new. Both sequences given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a similar method using DNA encoding the proteins with amino acids sequences of (I) and (II), or cells co-expressing the proteins or their partial peptide, optionally in the presence of animal-originated cartilage tissues or cells for co-culturing with a test compound, and measuring the proteoglycan decomposition activity with a control run for comparison; (2) kits for screening compounds or their salts promoting or inhibiting proteoglycan decomposition containing the proteins or their partial peptides, or DNA encoding them, or cells expressing them; (3) promoters or inhibitors of proteoglycan decomposition; (4) drugs containing the thus screened promoters or inhibitors; (5) preventives or remedies containing these screened compounds or their salts that inhibit or promote proteoglycan decomposition, or activity of the protein with an amino acid sequence of (I), its variant, their partial peptide or salts; (6) preventing or treating bone and joint diseases by administering an effective dose of the compounds or their salts inhibiting or promoting activity of the protein with an amino acid sequence of (I) or its derivative; and (7) the use of inhibitors or promoters of activity of the protein with an amino acid sequence of (I) or its derivative for producing preventives or remedies for bone and joint diseases.

ACTIVITY - Osteopathic. No biological data is given.

MECHANISM OF ACTION - None given.

USE - The method is promoters or inhibitors of proteoglycan decomposition as preventives or remedies for bone and joint diseases, e.g. rheumatoid arthritis, osteoporosis and arthritis deformans (all claimed).

ADMINISTRATION - Administration of the screened drugs is oral or non-oral, e.g. at 0.1-10 mg by injection

ADVANTAGE - With this method, the compounds regulating the decomposition activity of proteoglycan can be efficiently selected.

EXAMPLE - COS7 cells were transfected with readily-available expression vectors for human membrane-type (MT)3-matrix metalloproteinase (MMP) and MMP-19. Then, biological activity of the cells was assayed with bovine nose-isolated cartilage as substrate. No results are given.(96 pages)

L20 ANSWER 3 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-13531 BIOTECHDS
TITLE: Substances regulating the activity of proteins having increased expression in bone and joint disease for treatment and prevention of these diseases;
vector-mediated gene transfer useful for bone and cartilage formation disorder and development disorder gene therapy
AUTHOR: **HIKICHI Y**; INAZUKA M; **YOSHIMURA K**
PATENT ASSIGNEE: TAKEDA CHEM IND LTD
PATENT INFO: WO 2003022300 20 Mar 2003
APPLICATION INFO: WO 2002-JP9140 9 Sep 2002
PRIORITY INFO: JP 2001-303390 28 Sep 2001; JP 2001-273914 10 Sep 2001

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: WPI: 2003-313193 [30]

AB DERWENT ABSTRACT:

NOVELTY - Agents for the treating and preventing bone and joint diseases which regulate the activity or expression of human proteins (I) showing increased expression in diseased bone and joint tissue e.g. DIO2 (type 2 iodothyronine deiodinase); ANKH (pyrophosphate transporter); SHOX2 (short stature homeobox 2); TASK4 (potassium ion channel protein); EphA3 (Eph receptor A3); and/or MMP16 (matrix metalloproteinase 16), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for (1) agents for prevention and treatment of bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I); (2) diagnostic reagents for bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I); (3) screening agents for the treatment and prevention of bone and joint diseases, in which the effect of the test substance on the activity or expression of proteins (I) is determined; (4) kits for the screening method; (5) agents for the treatment and prevention of bone and joint diseases, identified by the method; (6) treatment and prevention of bone and joint diseases, using the agents of (5).

BIOTECHNOLOGY - Preferred Method: Regulation of the expression and activity of proteins (I) is preferably inhibition.

ACTIVITY - Antiarthritic; Antirheumatic; Osteopathic; Antiinflammatory.

MECHANISM OF ACTION - Iodothyronine deiodinase inhibitor; Pyrophosphate transport inhibitor; Short stature homeobox 2 inhibitor; Potassium ion transport inhibitor; Eph receptor antagonist; Matrix metalloproteinase 16 inhibitor.

USE - Prevention, treatment and diagnosis of diseases involving abnormal formation or development of bone and cartilage (such as arthritis deformans), chronic rheumatoid arthritis, synovial inflammation, or localized arthritis (such as 'tennis elbow').

ADMINISTRATION - 0.1-100, preferably 1-20 mg/day orally or 0.01-30, preferably 0.1-10 mg/day for a 60kg patient.

EXAMPLE - cDNA encoding human DIO2 is amplified from a human thyroid cDNA library and inserted into expression vector pcDNA3.1 (Invitrogen) to give pTB2249. COS7 cells are transfected with pTB2249 using FUGENE6 (Roche). The cells are cultured for two days then treated with trypsin and disrupted with ultrasound. Cell debris is removed and the supernatant treated with a test substance and with thyroxine (Sigma). After reaction at 37 degrees C for 1 hour, a Total T3 Radioimmunoassay Kit (Diagnostic Products) is used to assay the triiodothyronine formed. This is compared with the assay in the absence of test substance. This method is used to identify effective inhibitors of DIO2 activity, but no examples of actual substances so identified are given.(154 pages)

L20 ANSWER 4 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:829451 SCISEARCH
THE GENUINE ARTICLE: 723EF
TITLE: Microscopic polyangiitis associated with marked systemic bleeding tendency caused by disseminated intravascular coagulation
AUTHOR: Saito T (Reprint); Tsuchiya M; Shikata C; Yamaguchi H; Miyata S; Matsuo S; Ishizawa S; **Yoshimura K**
CORPORATE SOURCE: Jikei Univ, Sch Med, Div Diabet & Endocrinol, Dept Internal Med, Minato Ku, 3-25-8 Nishininbashi, Tokyo 1058461, Japan (Reprint); Jikei Univ, Sch Med, Aoto Hosp, Dept Internal Med, Div Resp & Infect Dis, Tokyo, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: INTERNAL MEDICINE, (SEP 2003) Vol. 42, No. 9, pp. 850-855. Publisher: JAPAN SOC INTERNAL MEDICINE, 34-3 3-CHOME HONGO BUNKYO-KU, TOKYO, 113, JAPAN.

ISSN: 0918-2918.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A 57-year-old woman was admitted to our hospital because of severe dyspnea due to pulmonary hemorrhage and rapidly progressive renal failure. The patient was positive for perinuclear pattern anti-neutrophil cytoplasmic antibody (p-ANCA) and was manifested with gastrointestinal bleeding and brain hemorrhage. Thus, she was diagnosed as having microscopic polyangiitis (MPA). Laboratory examination demonstrated severe thrombocytopenia, increased prothrombin time and a high concentration of fibrin degradation products. In addition, the elevated plasma levels of D-dimer, thrombin-antithrombin complex and plasmin-plasmin inhibitor complex led us to make a diagnosis of disseminated intravascular coagulation (DIC). Complication of DIC was considered to have caused further deterioration in bleeding tendency due to MPA in the present case. The patient was treated with plasma exchange, hemodialysis, administration of corticosteroid including pulse therapy and cyclophosphamide. Continuous infusion of gabexate mesilate proved effective for improvement of systemic bleeding tendency. However, she finally died of severe infectious diseases. In conclusion, it is suggested that ANCA-associated vasculitis could be accompanied by DIC and gabexate mesilate may be a useful therapeutic agent for these disorders.

L20 ANSWER 5 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:395595 BIOSIS
DOCUMENT NUMBER: PREV200300395595
TITLE: Peptide-lead nonpeptidic **protease** inhibitor targeting multi-drug resistant strains of HIV.
AUTHOR(S): Fujii, N. [Reprint Author]; Tamamura, H. [Reprint Author]; Yamasaki, T. [Reprint Author]; Otaka, A. [Reprint Author]; Koh, Y.; Aoki, M.; Maeda, K.; **Yoshimura, K.**; Mitsuya, H.
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan
SOURCE: Biopolymers, (2003) Vol. 71, No. 3, pp. 397. print.
Meeting Info.: 18th American Peptide Symposium on Peptide Revolution: Genomics, Proteomics and Therapeutics. Boston, MA, USA. July 19-23, 2003. American Peptide Society.
ISSN: 0006-3525 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003

L20 ANSWER 6 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:905367 SCISEARCH
THE GENUINE ARTICLE: 696GG
TITLE: Peptide-lead nonpeptidic **protease** inhibitor targeting multi-drug resistant strains of HIV
AUTHOR: Fujii N (Reprint); Tamamura H; Yamasaki T; Otaka A; Koh Y; Aoki M; Maeda K; **Yoshimura K**; Mitsuya H
CORPORATE SOURCE: Kyoto Univ, Grad Sch Pharmaceut Sci, Sakyo Ku, Kyoto 6068501, Japan; Kumamoto Univ, Sch Med, Dept Internal Med 2, Kumamoto 860, Japan; Kumamoto Univ, Ctr AIDS Res, Kumamoto 8608556, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: BIOPOLYMERS, (OCT 2003) Vol. 71, No. 3, pp. 397-397. MA P438.
Publisher: JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA.
ISSN: 0006-3525.

DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L20 ANSWER 7 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:129715 SCISEARCH
THE GENUINE ARTICLE: 641RW
TITLE: Effect of indinavir on the intestinal exsorption of amprenavir, saquinavir and nelfinavir after intravenous administration in rats
AUTHOR: Gao W H; Kageyama M; Inoue Y; Tadano J; Fukumoto K; Fukushima K; Yamasaki D; **Nishimura A**; Yoshikawa Y; Shibata N (Reprint); Takada K
CORPORATE SOURCE: Kyoto Pharmaceut Univ, Dept Pharmacokinet, Yamashina Ku, 5 Nakauchi Cho, Kyoto 6078414, Japan (Reprint); Kyoto Pharmaceut Univ, Dept Pharmacokinet, Yamashina Ku, Kyoto 6078414, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: BIOLOGICAL & PHARMACEUTICAL BULLETIN, (FEB 2003) Vol. 26, No. 2, pp. 199-204.
Publisher: PHARMACEUTICAL SOC JAPAN, 2-12-15-201 SHIBUYA, SHIBUYA-KU, TOKYO, 150, JAPAN.
ISSN: 0918-6158.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To elucidate drug interaction between human immunodeficiency virus (HIV) **protease** inhibitors (PIs), the effect of indinavir (IDV) on the intestinal exsorption of other HIV PIs, amprenavir (APV), saquinavir (SQV) and nelfinavir (NFV) was investigated in rats using an in situ single perfusion method. IDV in the intestinal perfusate inhibited the exsorption of rhodamine 123 (Rho123), a known P-glycoprotein (P-gp) substrate, from blood into intestinal lumen in a concentration-dependent manner, and the inhibitory potency of 10 mum IDV in the perfusate was close to that of 10 mum cyclosporin A (CsA) in the perfusate. Ten mum of IDV in the intestinal perfusate also decreased significantly the exsorption clearance of Rho123 after intravenous administration. The IDV concentration in this system was not likely to cause hepatic interaction between HIV PIs, because the plasma IDV concentration was far below its inhibition constants for other HIV PIs in the liver microsomes. Thus, 10 mum of IDV was chosen to investigate the effect of this inhibition on the exsorption of APV, SQV and NFV. IDV in the intestinal perfusate markedly increased the exsorbed amounts of SQV and NFV but not APV after intravenous administrations. Their exsorption clearances, however, showed only a slight increasing tendency or remained unchanged. These findings suggest that in addition to P-gp inhibition, other factors such as CYP3A inhibition might be important in the drug interaction of IDV with APV, SQV and NFV after intravenous administration in rat small intestine. The results obtained in this study will provide useful information to discuss the interactions among PIs when a double **protease** therapy is used for in HIV-infected patients.

L20 ANSWER 8 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:835493 SCISEARCH
THE GENUINE ARTICLE: 723HL
TITLE: The impact of highly active antiretroviral therapy by the oral route on the CD8 subset in monkeys infected chronically with SHIV89.6P
AUTHOR: **Yoshimura K**; Ido E; Akiyama H; Kimura T; Aoki M; Suzuki H; Mitsuya H; Hayami M; Matsushita S (Reprint)
CORPORATE SOURCE: Kumamoto Univ, Div Clin Retrovirol & Infect Dis, Ctr AIDS Res, 2-2-1 Honjo, Kumamoto 8600811, Japan (Reprint); Kumamoto Univ, Div Clin Retrovirol & Infect Dis, Ctr AIDS

Res, Kumamoto 8600811, Japan; Kumamoto Univ, Dept Internal Med 2, Kumamoto 8600811, Japan; Kyoto Univ, Inst Virus Res, Lab Viral Pathogenesis, Kyoto 6068507, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: JOURNAL OF VIROLOGICAL METHODS, (SEP 2003) Vol. 112, No. 1-2, pp. 121-128.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0166-0934.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 37
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of this study was to assess the impact of highly active antiretroviral therapy (HAART) by an oral route on the peripheral blood CD8 subset in the monkeys infected persistently with a pathogenic strain, SHIV89.6P. Two rhesus macaques were inoculated intravenously with SHIV89.6P, then treated with the combination of AZT, 3TC and Lopinavir/Ritonavir (LPV/RTV) as recommended in humans by the oral route with confectionery continued for 28 days. In one of two chronically infected macaques, MM260, the viral load was maintained in the range of 10(4) -10(5) copies/ml before HAART. The plasma viral load and proviral DNA decreased dramatically during the treatment, and cessation of this therapy the viral load rebounded to the pre-treatment level but the proviral DNA rebound was delayed. The other monkey, MM242, had low viral loads (1.2 x 10(3) < 5 x 10(2) copies/ml) both before and after HAART. CD4(+) and CD8(+) T cell counts and proviral DNA level were not significantly changed after the treatment. The percentages of CD8(+) CD45RA(-) Ki67(+) cells increased during (MM260) or after (MM242) HAART and the subset was maintained at a high percentage until 18 weeks post HAART in MM242. These findings suggest that this primate model might serve an important role in testing the virological and immunological efficacy of novel therapeutic strategies combined with HAART. (C) 2003 Elsevier B.V. All rights reserved.

on STN DUPLICATE 2
ACCESSION NUMBER: 2003004967 EMBASE
TITLE: LIGHT, a member of the tumor necrosis factor ligand superfamily, prevents tumor necrosis factor-α-mediated human primary hepatocyte apoptosis, but not Fas-mediated apoptosis.
AUTHOR: Matsui H.; **Hikichi Y.**; Tsuji I.; Yamada T.; Shintani Y.
CORPORATE SOURCE: Y. Shintani, Pharmacology Research Laboratories I, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Osaka 532-8686, Japan. Shintani_Yasushi@takeda.co.jp
SOURCE: Journal of Biological Chemistry, (20 Dec 2002) 277/51 (50054-50061).
Refs: 57
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB LIGHT is a member of tumor necrosis factor (TNF) superfamily, and its receptors have been identified as lymphotoxin-β receptor (LTβR) and the herpesvirus entry mediator (HVEM)/ATAR/TR2, both of which lack the cytoplasmic sequence termed the "death domain." The present study has demonstrated that LIGHT inhibits TNFα-mediated apoptosis of human

primary hepatocytes sensitized by actinomycin D (ActD), but not Fas- or TRAIL-mediated apoptosis. Furthermore, LIGHT does not prevent some cell lines such as HepG2 or HeLa from undergoing ActD/TNFα-induced apoptosis. This protective effect requires LIGHT pretreatment at least 3 h prior to ActD sensitization. LIGHT stimulates nuclear factor-κB (NF-κB)-dependent transcriptional activity in human hepatocytes like TNFα. The time course of NF-κB activation after LIGHT administration is similar to that of the pretreatment required for the anti-apoptotic effect of LIGHT. LIGHT inhibits caspase-3 processing on the apoptotic **protease** cascade in TNFα-mediated apoptosis but not Fas-mediated apoptosis. In addition, increased caspase-3 and caspase-8 activities in ActD/TNFα-treated cells are effectively blocked by LIGHT pretreatment. However, LIGHT does not change the expression of TNFRp55, TNFRp75, and Fas. These results indicate that LIGHT may act as an anti-apoptotic agent against TNFα-mediated liver injury by blocking the activation of both caspase-3 and caspase-8.

L20 ANSWER 10 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3

ACCESSION NUMBER: 2002313267 EMBASE
TITLE: Amino acid substitutions in Gag protein at non-cleavage sites are indispensable for the development of a high multitude of HIV-1 resistance against **protease** inhibitors.
AUTHOR: Gatanaga H.; Suzuki Y.; Tsang H.; **Yoshimura K.**; Kavlick M.F.; Nagashima K.; Gorelick R.J.; Mardy S.; Tang C.; Summers M.F.; Mitsuya H.
CORPORATE SOURCE: H. Mitsuya, Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, United States. hmitsuya@helix.nih.gov
SOURCE: Journal of Biological Chemistry, (22 Feb 2002) 277/8 (5952-5961).
Refs: 31
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Amino acid substitutions in human immunodeficiency virus type 1 (HIV-1) Gag cleavage sites have been identified in HIV-1 isolated from patients with AIDS failing chemotherapy containing **protease** inhibitors (PIs). However, a number of highly PI-resistant HIV-1 variants lack cleavage site amino acid substitutions. In this study we identified multiple novel amino acid substitutions including L75R, H219Q, V390D/V390A, R409K, and E468K in the Gag protein at non-cleavage sites in common among HIV-1 variants selected against the following four PIs: amprenavir, JE-2147, KNI-272, and UIC- 94003. Analyses of replication profiles of various mutant clones including competitive HIV-1 replication assays demonstrated that these mutations were indispensable for HIV-1 replication in the presence of PIs. When some of these mutations were reverted to wild type amino acids, such HIV-1 clones failed to replicate. However, virtually the same Gag cleavage pattern was seen, indicating that the mutations affected Gag protein functions but not their cleavage sensitivity to **protease**. These data strongly suggest that non-cleavage site amino acid substitutions in the Gag protein recover the reduced replicative fitness of HIV-1 caused by mutations in the viral **protease** and may open a new avenue for designing PIs that resist the emergence of PI-resistant HIV-1.

L20 ANSWER 11 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 2002:665387 SCISEARCH
THE GENUINE ARTICLE: 580KV
TITLE: Guanosine 5 '-diphosphate 3 '-diphosphate (ppGpp) synthetic activities on Escherichia coli SpoT domains
AUTHOR: Fujita C; **Nishimura A**; Iwamoto R; Ikehara K (Reprint)
CORPORATE SOURCE: Nara Womens Univ, Fac Sci, Dept Chem, Nara 6308506, Japan (Reprint); Natl Inst Genet Japan, Shizuoka 4118540, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: BIOSCIENCE BIOTECHNOLOGY AND BIOCHEMISTRY, (JUL 2002) Vol. 66, No. 7, pp. 1515-1523.
Publisher: JAPAN SOC BIOSCI BIOTECHN AGROCHEM, JAPAN ACAD SOC CTR BLDG, 2-4-6 YAYOI BUNKYO-KU, TOKYO, 113, JAPAN.
ISSN: 0916-8451.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Escherichia coli SpoT protein, with 702 amino acid residues, is a bifunctional enzyme catalyzing both guanosine 5'-diphosphate 3'-diphosphate (ppGpp) degradation and its synthesis. First, we investigated how many domains are included in SpoT protein, by limited hydrolysis of the protein with serine **proteases**, alpha-chymotrypsin, and elastase. Based on the results, we deduced that SpoT protein is composed of two major domains, an N-terminal half domain from Met1 to Phe373 and a C-terminal half domain from Glu374 to Asn702 (C-terminal end). In addition, by a further alpha-chymotrypsin digestion, two cleaved sites were found at Arg196 in the N-terminal half domain (D12) and at Lys475 in the C-terminal half domain (D34), to produce four minor domains, D1, D2, D3, and D4. Next, plasmids expressing the two major domains (D12 and D34) and four minor domains (D1, D2, D3, and D4) were constructed. Consequently, the deduced SpoT minor domains as well as the major domains were expressed as stable protein units, except for D4. D4 may also be folded into a stable protein in E. coli cells, since high expression of D4 from a plasmid results in host cell lethality. E. coli relA(-), spoT(-) double null strains expressing D1, D2, and D12 recovered cell growth in M9 minimal medium, but the transformants of D3, D4, and D34 did not grow in the minimal medium. This indicates that ppGpp synthetic activities could be restricted in the N-terminal half domain (D12, D1, and D2).

L20 ANSWER 12 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 4
ACCESSION NUMBER: 2002028070 EMBASE
TITLE: A potent human immunodeficiency virus type 1 **protease** inhibitor, UIC-94003 (TMC-126), and selection of a novel (A28S) mutation in the **protease** active site.
AUTHOR: **Yoshimura K.**; Kato R.; Kavlick M.F.; Nguyen A.; Maroun V.; Maeda K.; Hussain K.A.; Ghosh A.K.; Gulnik S.V.; Erickson J.W.; Mitsuya H.
CORPORATE SOURCE: H. Mitsuya, Medicine Branch, National Cancer Institute, Bldg. 10, Bethesda, MD 20892, United States. hmitsuya@helix.nih.gov
SOURCE: Journal of Virology, (2002) 76/3 (1349-1358).
Refs: 39
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We identified UIC-94003, a nonpeptidic human immunodeficiency virus (HIV)

protease inhibitor (PI), containing 3(R),3a(S),6a(R)-bis-tetrahydrofuranyl urethane (bis-THF) and a sulfonamide isostere, which is extremely potent against a wide spectrum of HIV (50% inhibitory concentration, 0.0003 to 0.0005 μM). UIC-94003 was also potent against multi-PI-resistant HIV-1 strains isolated from patients who had no response to any existing antiviral regimens after having received a variety of antiviral agents (50% inhibitory concentration, 0.0005 to 0.0055 μM). Upon selection of HIV-1 in the presence of UIC-94003, mutants carrying a novel active-site mutation, A28S, in the presence of L10F, M46I, I50V, A71V, and N88D appeared. Modeling analysis revealed that the close contact of UIC-94003 with the main chains of the **protease** active-site amino acids (Asp29 and Asp30) differed from that of other PIs and may be important for its potency and wide-spectrum activity against a variety of drug-resistant HIV-1 variants. Thus, introduction of inhibitor interactions with the main chains of key amino acids and seeking a unique inhibitor-enzyme contact profile should provide a framework for developing novel PIs for treating patients harboring multi-PI-resistant HIV-1.

L20 ANSWER 13 OF 37 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001520431 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11454872
TITLE: Novel low molecular weight spirodiketopiperazine derivatives potently inhibit R5 HIV-1 infection through their antagonistic effects on CCR5.
AUTHOR: Maeda K; **Yoshimura K**; Shibayama S; Habashita H; Tada H; Sagawa K; Miyakawa T; Aoki M; Fukushima D; Mitsuya H
CORPORATE SOURCE: Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto 860-0811, Japan.
SOURCE: Journal of biological chemistry, (2001 Sep 14) 276 (37) 35194-200.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010925
Last Updated on STN: 20030105
Entered Medline: 20011011

AB Novel low molecular weight spirodiketopiperazine derivatives which potently inhibit R5 human immunodeficiency virus type 1 (HIV-1) infection through their antagonistic effects on CCR5 were identified. One such compound E913 (M(r) 484) specifically blocked the binding of macrophage inflammatory protein-1alpha (MIP-1alpha) to CCR5 (IC(50) 0.002 microm) and MIP-1alpha-elicited cellular Ca(2+) mobilization (IC(50) approximately 0.02 microm). E913 potently inhibited the replication of laboratory and primary R5 HIV-1 strains as well as various multidrug-resistant monocyte/macrophage tropic (R5) HIV-1 at IC(50) values of 0.03 to 0.06 microm. E913 was inactive against T cell tropic (X4) HIV-1; however, when combined with a CXCR4 antagonist AMD-3100, E913 potently and synergistically inhibited the replication of dualtropic HIV-1 and a 50:50 mixture of R5 and X4 HIV-1. Antagonism in anti-HIV-1 activity was not seen when E913 was combined with the reverse transcriptase inhibitor zidovudine or **protease** inhibitors. E913 proved to compete with the binding of antibodies to CCR5 which recognize the C-terminal half of the second extracellular loop (ECL2B) of CCR5. E913 and its analogs are acid-resistant and orally bioavailable in rodents. These data warrant that spirodiketopiperazine derivatives be further developed as potential therapeutics for HIV-1 infection.

L20 ANSWER 14 OF 37 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001232406 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11164251
TITLE: A novel monoclonal antibody K1 recognises early neurones in the rat cortex.
AUTHOR: Ishii K; Murata A; **Yoshimura K**; Uyemura K
CORPORATE SOURCE: Department of Physiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
SOURCE: Neuroscience research, (2001 Jan) 39 (1) 31-7. Journal code: 8500749. ISSN: 0168-0102.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB The aim of this study was to produce monoclonal antibodies specific for neurones that are generated earliest in the rat neocortex. One of the established clones, K1, showed a strong immunoreactivity in the marginal zone at the 19th day of gestation (E19). The immunoreactivity of K1 initially appeared in the primordial plexiform layer at E15, in the subplate at E16, and in the marginal zone by E17. It became undetectable in the first postnatal week. The immunoreactivity was not detected in the neocortex of adults or elderly. Western blotting analysis revealed reactive bands at positions corresponding to proteins of 290 and 280 kDa for the neocortical membrane fractions prepared from E16 to E21 embryos. In these stages, smears of bands were also found at positions corresponding to higher molecular weights. A single band of protein of 280 kDa was detected for the soluble fractions prepared from the embryos at E19 and E21. These reactivities were susceptible to **protease** , but not to enzymatic or chemical destruction of carbohydrate residues. Electron microscopic analysis showed that the K1 immunoreactivity was detected primarily on the cellular membranes of neurites. In the marginal zone at E19, the K1 immunoreactivity was localised where neurites make contact with other neurites or somata. A portion of these contact points had typical features of synapses. In the cortical plate of the same stage, arrays of tiny K1-immunoreactive puncta were observed on a subset of radial processes. These results suggest that monoclonal antibody K1 is a marker recognising neurites of subplate neurones that extend radially and make neuronal contacts in the marginal zone.

L20 ANSWER 15 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2000-07820 BIOTECHDS
TITLE: Novel protein belong to A **disintegrin** and metallo **protease** family, with **protease** activity and extracellular matrix digesting enzyme activity for diagnosis and drug development;
recombinant protein production via vector-mediated gene transfer and expression in host cell for e.g. hepatic fibrosis diagnosis, prevention and therapy
AUTHOR: **Yoshimura K; Hikichi Y; Nishimura A**
PATENT ASSIGNEE: Takeda-Chem.
LOCATION: Osaka, Japan.
PATENT INFO: WO 2000014227 16 Mar 2000
APPLICATION INFO: WO 1999-JP4766 2 Sep 1999
PRIORITY INFO: JP 1998-250115 3 Sep 1998
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2000-271056 [23]

AB A protein (I), which belongs to the A **disintegrin** and metallo **protease** family and is encoded by a 96 amino acid protein sequence (specified), or its salt, is new. Also claimed are: a protein

fragment of (I) or its salt, encoded by a 10 amino acid protein sequence (II) (specified); a DNA encoding (I); a DNA (III) encoded by a 288 bp sequence (specified) which encodes a fragment of (I); a recombinant vector containing the DNA which encodes (I); a host cell transformed with the vector; producing (I) by culturing the transformed cells; an antibody specific for (I); a diagnostic reagent containing the DNA encoding (I) or the antibody; a drug containing (I) for preventing or treating e.g. sciatica or osteopetrosis; and a screening method for identifying inhibitors or promoters of **protease** and extracellular matrix digesting enzyme. The above may be useful for the diagnosis, prevention and treatment (via drug development) of diseases such as intervertebral hernia, glomerulitis, diabetic nephropathy, hepatic fibrosis or pulmonary fibrosis. (I) is preferably encoded by a 504 or 775 amino acid protein sequence and a 1,620 or 2,325 bp DNA sequence (all specified). (108pp)

L20 ANSWER 16 OF 37 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000240045 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10775598
TITLE: Identification of a key target sequence to block human immunodeficiency virus type 1 replication within the gag-pol transframe domain.
AUTHOR: Sei S; Yang Q E; O'Neill D; **Yoshimura K**; Nagashima K; Mitsuya H
CORPORATE SOURCE: HIV Clinical Interface Laboratory, SAIC-Frederick, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702, USA.. SEI@dtpax2.ncifcrf.gov
CONTRACT NUMBER: NO1-CO-56000 (NCI)
SOURCE: Journal of virology, (2000 May) 74 (10) 4621-33. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511

AB Although the full sequence of the human immunodeficiency virus type 1 (HIV-1) genome has been known for more than a decade, effective genetic antivirals have yet to be developed. Here we show that, of 22 regions examined, one highly conserved sequence (ACTCTTTGGCAACGA) near the 3' end of the HIV-1 gag-pol transframe region, encoding viral **protease** residues 4 to 8 and a C-terminal Vpr-binding motif of p6(Gag) protein in two different reading frames, can be successfully targeted by an antisense peptide nucleic acid oligomer named PNA(PR2). A disrupted translation of gag-pol mRNA induced at the PNA(PR2)-annealing site resulted in a decreased synthesis of Pr160(Gag-Pol) polyprotein, hence the viral **protease**, a predominant expression of Pr55(Gag) devoid of a fully functional p6(Gag) protein, and the excessive intracellular cleavage of Gag precursor proteins, hindering the processes of virion assembly. Treatment with PNA(PR2) abolished virion production by up to 99% in chronically HIV-1-infected H9 cells and in peripheral blood mononuclear cells infected with clinical HIV-1 isolates with the multidrug-resistant phenotype. This particular segment of the gag-pol transframe gene appears to offer a distinctive advantage over other regions in invading viral structural genes and restraining HIV-1 replication in infected cells and may potentially be exploited as a novel antiviral genetic target.

L20 ANSWER 17 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:878748 SCISEARCH
THE GENUINE ARTICLE: 374HR
TITLE: Syntheses of 4'-C-ethynyl-beta-D-arabino- and 4'-C-ethynyl-2'-deoxy-beta-D-ribo-pentofuranosylpyrimidines and -purines and evaluation of

their anti-HIV activity

AUTHOR: Ohrui H (Reprint); Kohgo S; Kitano K; Sakata S; Kodama E; **Yoshimura K**; Matsuoka M; Shigeta S; Mitsuya H

CORPORATE SOURCE: TOHOKU UNIV, GRAD SCH AGR SCI, DIV LIFE SCI, AOBA KU, 1-1 TSUTSUMIDORI AMAMIYAMACHI, SENDAI, MIYAGI 9818555, JAPAN (Reprint); YAMASA CORP, DIV BIOCHEM, CHIBA 2880056, JAPAN; KYOTO UNIV, INST VIRUS RES, AIDS RES CTR, LAB VIRUS IMMUNOL, KYOTO 6068507, JAPAN; FUKUSHIMA MED UNIV, DEPT MICROBIOL, FUKUSHIMA 9601295, JAPAN; KUMAMOTO UNIV, SCH MED, DEPT INTERNAL MED 2, KUMAMOTO 860, JAPAN; NCI, DIV CLIN SCI, MED BRANCH, EXPT RETROVIROL SECT, BETHESDA, MD 20892

COUNTRY OF AUTHOR: JAPAN; USA

SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (16 NOV 2000) Vol. 43, No. 23, pp. 4516-4525.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 0022-2623.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 29

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 4'-C-Ethynyl-beta -D-arabino- and 4'-C-ethynyl-2'-deoxy-beta -D-ribo-pentofuranosylpyrine and -purine nucleosides were synthesized and evaluated for their in vitro anti-HIV activity. The key intermediate, 4-C-ethynyl- or 4-C-triethylsilylethynyl-D-ribo-pentofuranose, was prepared from D-glucose and glycosidated with various pyrimidine or purine bases. The arabino pyrimidine derivatives were prepared from the corresponding ribo derivatives via O-2,2'-anhydro nucleosides. The 2'-deoxy-ribo derivatives were synthesized by radical reduction of 2'-bromo or 2'- phenoxythiocarbonyloxy nucleosides. Among these 4'-C-ethynyl nucleosides, seven analogues proved to be potent against HIV-1 in vitro with EC50 values ranging from 0.0003 to 0.03 muM. These compounds also exerted activity against clinical and multi-dideoxy-nucleoside-resistant HIV-1 strains with comparable EC50 values. Three such 4'-C-ethynyl-2'-deoxypurine analogues including 4'-C-ethynyl-2'-deoxyadenosine and 4'-C-ethynyl-2,6-diamino-2'-deoxy-purine were less cytotoxic [selectivity indices (SIs): 975-2733] than three 4'-C-ethynyl-2-deoxycytidine analogues (SIs: 63-363). 4'-C-Ethynyl-5-fluoro-2'-deoxycytidine was least toxic (SI: >3333) and potent against all HIV strains tested.

L20 ANSWER 18 OF 37 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 2000137776 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10671334

TITLE: Combination therapy with amprenavir, abacavir, and efavirenz in human immunodeficiency virus (HIV)-infected patients failing a **protease**-inhibitor regimen: pharmacokinetic drug interactions and antiviral activity.

AUTHOR: Falloon J; Piscitelli S; Vogel S; Sadler B; Mitsuya H; Kavlick M F; **Yoshimura K**; Rogers M; LaFon S; Manion D J; Lane H C; Masur H

CORPORATE SOURCE: National Institute of Allergy and Infectious Diseases, Bethesda, MD, 20892-1880, USA.. jfalloon@nih.gov

SOURCE: Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, (2000 Feb) 30 (2) 313-8.
Journal code: 9203213. ISSN: 1058-4838.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000412

AB Patients with plasma viral RNA >50,000 copies/mL, despite a **protease**-inhibitor regimen, received abacavir, amprenavir, and efavirenz to assess efavirenz-amprenavir drug interactions and to evaluate safety and antiviral response. Patients first received amprenavir with abacavir and other nucleoside analogs. Amprenavir levels were measured before and after adding efavirenz. Patients then received a second **protease** inhibitor. There was evidence of genotypic and phenotypic resistance at study entry. No patient had study drugs discontinued because of toxicity. Efavirenz decreased the steady-state area under the curve, maximum plasma concentration, and minimum plasma concentration of amprenavir by 24%, 33%, and 43%, respectively. Three of 10 patients had >1.5 log10 viral response to abacavir and amprenavir. All 8 patients who added efavirenz had >0.5 log10 decline in viral load, and this response lasted >24 weeks for 3 of the patients. A combination regimen that included abacavir, amprenavir, and efavirenz was well tolerated and had sustained activity in some patients. Concomitant efavirenz therapy decreases amprenavir concentrations.

L20 ANSWER 19 OF 37 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 1999342077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10411934
TITLE: JE-2147: a dipeptide **protease** inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1.
AUTHOR: **Yoshimura K**; Kato R; Yusa K; Kavlick M F; Maroun V; Nguyen A; Mimoto T; Ueno T; Shintani M; Falloon J; Masur H; Hayashi H; Erickson J; Mitsuya H
CORPORATE SOURCE: Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 Jul 20) 96 (15) 8675-80. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990823

AB We designed, synthesized, and identified JE-2147, an allophenylnorstatine-containing dipeptide HIV **protease** inhibitor (PI), which is potent against a wide spectrum of HIV-1, HIV-2, simian immunodeficiency virus, and various clinical HIV-1 strains in vitro. Drug-resistant clinical HIV-1 strains, isolated from seven patients who had failed 9-11 different anti-HIV therapeutics after 32-83 months, had a variety of drug-resistance-related amino acid substitutions and were highly and invariably resistant to all of the currently available anti-HIV agents. JE-2147 was, however, extremely potent against all such drug-resistant strains, with IC(50) values ranging from 13-41 nM (<2-fold changes in IC(50) compared with that of wild-type HIV-1). The emergence of JE-2147-resistant HIV-1 variants in vitro was substantially delayed compared with that of HIV-1 resistant to another allophenylnorstatine-containing compound, KNI-272, and other related PIs. Structural analysis revealed that the presence of a flexible P2' moiety is important for the potency of JE-2147 toward wild-type and mutant viruses. These data suggest that the use of flexible components may open a new avenue for designing PIs that resist the emergence of PI-resistant HIV-1. Further development of JE-2147 for treating patients harboring multi-PI-resistant HIV-1 is warranted.

L20 ANSWER 20 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 1998-04802 BIOTECHDS
TITLE: Fas ligand-like protein with apoptosis inducing activity; vector expression in mouse and application in therapy
AUTHOR: Nishi K; **Hikichi Y**; Shintani Y
PATENT ASSIGNEE: Takeda-Chem.
LOCATION: Osaka, Japan.
PATENT INFO: WO 9803648 29 Jan 1998
APPLICATION INFO: WO 1997-JP2480 17 Jul 1997
PRIORITY INFO: JP 1997-19330 31 Jan 1997; JP 1996-191204 19 Jul 1996
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1998-120773 [11]

AB A Fas ligand-like protein (Pr1) with apoptosis inducing activity of given 240 or 239 amino acid protein sequence, a partial protein or its salt, is claimed. A DNA sequence (DNA1, preferably of the sequences given) encoding Pr1, a recombinant vector containing DNA1 and a host (preferably a mouse) transformed with the vector is claimed. A non-human mammalian embryonic stem cell where DNA1 is inactivated and a non-human mammal (preferably a mouse) deficient in DNA1 expression are claimed. An antibody against Pr1 is claimed. Methods are claimed for screening for a compounds capable of changing the Pr1 receptor-binding activity or enhancing or inhibiting an intracellular signal transduction after Pr1 binding. Methods are claimed for screening for compounds which promote or inhibit the activity of a **protease** able to convert Pr1, or the activity of a promoter against DNA1. Pr1 and the enhancers of **protease** activity, intracellular signal transduction, or promoter activity can be used to treat e.g. cancer, viral infection, hepatitis, bone disease or atherosclerosis. The inhibitors can be used to treat e.g. AIDS, rheumatism, and inflammation. (120pp)

L20 ANSWER 21 OF 37 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1999000693 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9784105
TITLE: Synthesis of peptide aldehyde derivatives as selective inhibitors of human cathepsin L and their inhibitory effect on bone resorption.
AUTHOR: Yasuma T; Oi S; Choh N; Nomura T; Furuyama N; **Nishimura A**; Fujisawa Y; Sohda T
CORPORATE SOURCE: Pharmaceutical Research Division and Discovery Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-Chome, Yodogawa-ku, Osaka 532-8686, Japan.. YASUMA_TSUNEO@takeda.co.jp
SOURCE: Journal of medicinal chemistry, (1998 Oct 22) 41 (22) 4301-8.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20020420
Entered Medline: 19981123

AB Cathepsin L, a lysosomal cysteine **protease**, is secreted by osteoclasts and participates in bone collagen degradation. In a search for cathepsin L inhibitors as antiosteoporotic agents, a series of peptide aldehyde derivatives were prepared by two synthetic approaches, DMSO oxidation of the corresponding alcohol derivatives and DIBAL-H reduction of the corresponding N, O-dimethylhydroxylamide derivatives, and evaluated for inhibitory activity against human cathepsin L and for inhibitory effects on bone resorption. Some of the peptide aldehyde derivatives including alpha-acylamino aldehyde derivatives showed potent activities.

Among these compounds, N-(1-naphthalenylsulfonyl-L-isoleucyl-L-tryptophanal (12) was selected as a candidate for further investigation. Compound 12, a potent, selective, and reversible inhibitor of human cathepsin L with an IC50 of 1.9 nM, inhibited the release of Ca2+ and hydroxyproline from bone in in vitro bone culture system and also prevented bone loss in ovariectomized mice at an oral dose of 50 mg/kg.

L20 ANSWER 22 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 1998-00877 BIOTECHDS
TITLE: New matrix metallo **protease** from human or rat, related DNA, vectors, transformed cells; for use in therapy or gene therapy
AUTHOR: **Yoshimura K; Hikichi Y; Nishimura A**
PATENT ASSIGNEE: Takeda-Chem.
LOCATION: Osaka, Japan.
PATENT INFO: WO 9740157 30 Oct 1997
APPLICATION INFO: WO 1997-JP1433 24 Apr 1997
PRIORITY INFO: JP 1996-104902 25 Apr 1996
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1997-535841 [49]
AB A new protein (I) (and its salt and equivalents) has a 508 amino acid sequence, preferably of human origin. Also new are: active fragments (Ia) of (I), preferably 411, 416, 419, and 424 amino acid fragments; DNA (II) encoding (I); recombinant vectors containing (II); cells transformed with the vectors; and antibodies against (I) and (Ia). A new method involves screening for proteolytic activity in the presence and absence of a compound against a substrate. The protein or DNA may be used in therapy or gene therapy of diabetic nephropathy, glomerulonephritis, lung fibrosis, hepatolienal fibrosis, liver cirrhosis, osteopetrosis or herniated disk (claimed). In an example, an ss cDNA library from human liver was screened with a biotinylated DNA probe. The selected DNA was eluted from magnetic beads, a second strand was synthesized using a DNA primer, and the product was used to transform Escherichia coli DH10B. The transformants were subjected to colony polymerase chain reaction, and DNA from colonies that produced a 510 bp fragment containing a 2264 bp insert was sequenced. Plasmid pTB1921 containing the insert was transiently expressed in COS-7 cells. (117pp)

L20 ANSWER 23 OF 37 MEDLINE on STN
ACCESSION NUMBER: 96435201 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8838087
TITLE: Structure and expression of the human neutrophil elastase gene--regulatory mechanism and its relevance to the respiratory diseases.
AUTHOR: **Yoshimura K**; Tanabe O
CORPORATE SOURCE: Department of Gene Therapy, Jikei University School of Medicine.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (1996 Feb) 54 (2) 396-404. Ref: 24
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19980206
Entered Medline: 19961127
AB Human neutrophil elastase is a 29 kDa, 220-residue single chain glycoprotein which functions as a powerful serine **protease**.

Because NE is capable of destroying a broad range of substrates including cross-linked elastin and the major forms of collagen as well as the cell walls of gram-negative bacilli, it possesses the two-edged sword property that is required for normal tissue turnover and host defense, yet potentially harmful in its ability to destroy normal tissues simultaneously. In this regard, NE plays a central role in the pathogenesis of pulmonary emphysema by destroying the alveolar walls of the lung in the conditions that antiproteases in the lung such as alpha 1-antitrypsin (alpha 1-AT) are inactivated-e.g., cigarette smoking, or alpha 1-AT deficiency caused by mutations of the alpha 1-AT gene-resulting in excess burden of NE in the lung. The gene encoding the NE protein has 5 exons and is located at chromosome 19p13.3. Expression of the NE gene is tightly controlled mainly at the transcriptional level, and limited to the early stage of myeloid cell differentiation in bone marrow cells, mostly in promyelocytes. The knowledge on the modulation of lineage- and differentiation-specific NE gene expression could offer the possible therapeutic strategy to the diseases such as pulmonary emphysema.

L20 ANSWER 24 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:455837 SCISEARCH
THE GENUINE ARTICLE: NW496
TITLE: MODULATION OF SECRETORY LEUKOPROTEASE INHIBITOR GENE-EXPRESSION IN HUMAN BRONCHIAL EPITHELIAL-CELLS BY PHORBOL EATER
AUTHOR: MARUYAMA M; HAY J G; **YOSHIMURA K**; CHU C S; CRYSTAL R G (Reprint)
CORPORATE SOURCE: NHLBI, PULM BRANCH, BLDG 10, ROOM 6D03, BETHESDA, MD, 20892 (Reprint); NHLBI, PULM BRANCH, BETHESDA, MD, 20892; CORNELL UNIV, COLL MED, DIV PULM & CRIT CARE MED, NEW YORK, NY, 10021
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (JUL 1994) Vol. 94, No. 1, pp. 368-375.
ISSN: 0021-9738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 65

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Secretory leukoprotease inhibitor (SLPI), a 12-kD nonglycosylated serine antiprotease, helps to protect the epithelial surface of the airways from the destructive capacity of neutrophil elastase. Based on the recognition that SLPI levels can increase in the presence of airway inflammation, we hypothesized that inflammatory stimuli should modulate the expression of the SLPI gene in airway epithelial cells. To evaluate this, the modulation of SLPI gene expression with various inflammatory stimuli was evaluated in the HS-24 human bronchial epithelial cell line. After preliminary studies showed that several inflammatory mediators enhanced SLPI messenger RNA (mRNA) levels, PMA was used as a model inflammatory stimulus. PMA significantly increased the level of 0.7-kb SLPI mRNA transcripts in HS-24 cells in a dose- and time-dependent fashion and increased the amount of SLPI protein in the culture supernatant. Nuclear run-on analyses showed that the SLPI gene transcription rate increased approximately twofold after PMA stimulation. Transfection studies using fusion genes composed of fragments of up to 1.2 kb of the 5' flanking sequence of the SLPI gene and a luciferase reporter gene demonstrated potent promoter activity in the 131-bp segment (-115 to +16 relative to the transcription start site), and all longer segments up to 1.2 kb, whereas smaller segments showed low promoter activity. An 18-bp element (-98 to -115), in a region with homology to PMA-responsive regions in the Moloney murine leukemia virus enhancer and the IL-8 gene, was shown to be of importance in the level of transcription of the SLPI gene. However, this element was not responsible for the upregulation of SLPI gene expression by PMA. Evaluation of HS-24 cells in the presence of

actinomycin D demonstrated that SLPI mRNA transcripts were very stable and became more so in the presence of PMA. Thus, SLPI gene expression in airway epithelial cells can be upregulated by an inflammatory stimulus, and this modulation is regulated at both the transcriptional and posttranscriptional levels. These mechanisms of SLPI upregulation likely play a role in defending the epithelial surface in the local milieu of inflammatory lung disease.

L20 ANSWER 25 OF 37 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 94063994 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8244451
TITLE: Intestinal protection against Strongyloides ratti and mastocytosis induced by administration of interleukin-3 in mice.
AUTHOR: Abe T; Sugaya H; Ishida K; Khan W I; Tasdemir I; **Yoshimura K**
CORPORATE SOURCE: Department of Parasitology, Akita University School of Medicine, Japan.
SOURCE: Immunology, (1993 Sep) 80 (1) 116-21.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19940201
Entered Medline: 19931223

AB Information about interleukin-3 (IL-3) effects in vivo is limited compared with the in vitro effects. We found that a repetitive injection of a low dose of recombinant IL-3 induced protection against intestinal worms of Strongyloides ratti in C57BL/6 mice. When mice were injected i.p. with different doses of recombinant IL-3 twice a day from day -5 to day -1 and infected orally with larvae recovered from the head of infected rats on day 0, worm recovery from the small intestine was markedly reduced by a total of 10(4) U IL-3 or more on day 2 post-infection. The number of intestinal mucosal mast cells (MMC) was increased by the protective dose of IL-3. The IL-3 treatment, however, was ineffective in protecting mice against tissue migrating larvae, as assessed by recovery from the head. The protective effect of IL-3 on intestinal worms was observed within 6 hr post oral infection, suggesting little concern with antigen-specific immune responses. The effective dose of IL-3 treatment increased the number of MMC progenitors five times in the spleen and the mesenteric lymph nodes. An MMC-specific **protease**, MMCP-1, was secreted 200 times more than in controls in the intestinal lumen by the IL-3 treatment. The IL-3 treatment induced no protection or mastocytosis in mast cell-deficient W/Wv mice. These results suggest that the IL-3-induced intestinal protection against S. ratti is mediated by MMC.

L20 ANSWER 26 OF 37 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 94276366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8007466
TITLE: Pathogenesis of idiopathic interstitial pneumonia/idiopathic pulmonary fibrosis: cellular and molecular biology of the disease.
AUTHOR: **Yoshimura K**
CORPORATE SOURCE: Department of Internal Medicine II, Daisan Hospital, Jikei University School of Medicine, Tokyo, Japan.
SOURCE: Nihon Kyobu Shikkan Gakkai zasshi, (1993 Dec) 31 Suppl 20-31. Ref: 59
Journal code: 7505737. ISSN: 0301-1542.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 19990129
Entered Medline: 19940721

AB Idiopathic interstitial pneumonia (IIP), which is referred to as "idiopathic pulmonary fibrosis (IPF)" in US and European countries or "cryptogenic fibrosing alveolitis (CFA)" in UK, is considered to result from an uncontrolled, chronic inflammatory process in the lower respiratory tract and alveoli of the lung. It is conceivable that some hereditary background may contribute to the disease in susceptible individuals. In IPF, alveolitis involving activation of alveolar macrophages (AM), neutrophils, T- and B-lymphocytes and/or other inflammatory cell types precedes the injury to the lung parenchyma and interstitial fibrosis. Activation and accumulation of cellular components in the disease seem to be modulated by a variety of biological substances such as cytokines, chemotactic factors and adhesion molecules. Exposure to inorganic dusts or viral infection also may trigger activation of AM. The injury to the alveolar epithelium, capillary endothelial cells and extracellular matrix mediated by oxidants and/or **proteases** produced by AM and neutrophils results in the derangement of the lung parenchyma. Subsequent fibrotic change of the lung interstitium is characterized by the accumulation of mesenchymal cells such as fibroblasts and deposition of their connective tissue produces within the alveolar walls. In this process, AM is considered to play a major role by secreting growth factors for mesenchymal cells, although alveolar epithelial and endothelial cells also seem to participate in activating mesenchymal cell proliferation in IPF. Possibly, connective tissue synthesis and/or degradation may be altered in the process of IPF, although there is no direct evidence for this so far. Thus, IPF is a chronic inflammatory disease in which inflammatory processes of the alveoli injure the lung parenchyma and modulate the proliferation of mesenchymal cells which result in the fibrotic change. The pathogenesis of the disease involves multiple cellular components of the lower respiratory tract through modulation of gene expression and protein synthesis of a variety of biological factors.

L20 ANSWER 27 OF 37 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 92265930 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1586720
TITLE: Transcriptional and posttranscriptional modulation of human neutrophil elastase gene expression.
AUTHOR: **Yoshimura K**; Crystal R G
CORPORATE SOURCE: Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892.
SOURCE: Blood, (1992 May 15) 79 (10) 2733-40.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 20000303
Entered Medline: 19920619

AB Human neutrophil elastase (NE), a 29-Kd potent serine **protease** stored in azurophilic granules of mature neutrophils, is coded for by the NE gene, a single copy gene with 5 exons spanning a 6-kb segment of chromosome 11 at q14. With the knowledge that the NE gene expression is limited to early myeloid cell differentiation, mechanisms modulating expression of the NE gene were evaluated in the HL-60 promyelocytic

leukemia cell line, a model of early bone marrow precursor cells. Consistent with the presence of NE messenger RNA (mRNA) transcripts in undifferentiated HL-60 cells, nuclear transcription run-on analyses showed that HL-60 cells actively transcribed the NE gene. However, the transcription rate of the NE gene was relatively low, only 40% of the myeloperoxidase gene, a gene expressed in parallel with NE. When induced toward the mononuclear phagocytic lineage with phorbol 12-myristate 13-acetate (PMA), HL-60 cells exhibited marked suppression of NE gene transcription, declining to 17% of the resting rate within 2 days. Induction toward mononuclear phagocytic lineage differentiation caused no change in NE mRNA transcript half-life (T1/2), but mRNA levels decreased markedly over time, with levels undetectable 1.5 days after PMA stimulation. In contrast, when induced toward the myelocytic lineage with dimethyl sulfoxide, the rate of NE gene transcription increased 1.9-fold within 5 days. Interestingly, the mRNA transcript levels increased 2.5-fold by 5 days despite the fact that induction toward myelocytic lineage differentiation was accompanied by a marked reduction of NE mRNA transcript T1/2. Together, these observations suggest that the NE gene expression during bone marrow differentiation is modulated mainly at the transcriptional level, with some posttranscriptional modulation contributing, particularly during myelocytic lineage differentiation.

L20 ANSWER 28 OF 37 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 92235262 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1569186
TITLE: Neutrophil elastase in respiratory epithelial lining fluid of individuals with cystic fibrosis induces interleukin-8 gene expression in a human bronchial epithelial cell line.
AUTHOR: Nakamura H; **Yoshimura K**; McElvaney N G; Crystal R G
CORPORATE SOURCE: Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.
SOURCE: Journal of clinical investigation, (1992 May) 89 (5) 1478-84.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920612
Last Updated on STN: 20000303
Entered Medline: 19920526

AB The respiratory manifestations of cystic fibrosis (CF) are characterized by neutrophil-dominated airway inflammation. Since a variety of inflammatory stimuli are capable of inducing bronchial epithelial cells to express the gene for IL-8, a cytokine that attracts and activates neutrophils, mediators in respiratory epithelial lining fluid (ELF) of CF individuals might induce IL-8 production by epithelial cells, thus recruiting neutrophils to the airways. BET-1A human bronchial epithelial cells at rest or incubated with normal ELF showed little IL-8 gene expression, but after incubation with CF ELF, a marked increase in IL-8 transcript levels was observed. CF ELF contained high levels of neutrophil elastase (NE) and various serine **protease** inhibitors prevented CF ELF from inducing IL-8 gene expression in BET-1A cells, suggesting that NE was the dominant inducer for IL-8 production in CF ELF. The addition of purified NE caused BET-1A cells to increase IL-8 gene transcription with accumulation of mRNA transcripts and to release IL-8-like neutrophil chemotactic activity. These observations suggest a self-perpetuating inflammatory process on the CF bronchial surface where NE released by neutrophils induced the bronchial epithelium to secrete IL-8, which in turn recruits additional neutrophils to the bronchial surface.

L20 ANSWER 29 OF 37 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 92348836 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1640091
TITLE: **Protease** resistant interleukin-3 stimulating components in excretory and secretory products from adult worms of Strongyloides ratti.
AUTHOR: Abe T; Nawa Y; **Yoshimura K**
CORPORATE SOURCE: Department of Parasitology, Akita University School of Medicine, Japan.
SOURCE: Journal of helminthology, (1992 Jun) 66 (2) 155-8. Journal code: 2985115R. ISSN: 0022-149X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920911
Last Updated on STN: 20000303
Entered Medline: 19920903

AB Excretory and secretory (ES) products collected from adult worms of Strongyloides ratti stimulated interleukin-3 (IL-3) production with mesenteric lymph node cells from infected C57BL/6 mice, but not with normal mesenteric lymph node cells. The IL-3 stimulating components were not major IgG binding antigens. Activity of the IL-3 stimulating components was stable by treatment with **protease**, although reduced by heating in boiling water.

L20 ANSWER 30 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:335911 SCISEARCH
THE GENUINE ARTICLE: FP851
TITLE: EXPRESSION OF THE SECRETORY LEUKOPROTEASE INHIBITOR GENE IN EPITHELIAL-CELLS
AUTHOR: ABE T; KOBAYASHI N; **YOSHIMURA K**; TRAPNELL B C; KIM H; HUBBARD R C; BREWER M T; THOMPSON R C; CRYSTAL R G (Reprint)
CORPORATE SOURCE: NHLBI, PULM BRANCH, BLDG 10, ROOM 6D03, BETHESDA, MD, 20892; SYNERGEN, BOULDER, CO, 80301
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1991) Vol. 87, No. 6, pp. 2207-2215.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 51

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The secretory leukoprotease inhibitor (SLPI) gene codes for a 12-kD protein that within the lung protects the airway epithelium from neutrophil elastase. Screening of 228 alleles in 114 individuals for sequence differences by RNase protection of genomic DNA revealed no detectable polymorphisms in SLPI gene exons II-IV. SLPI gene expression in the lung was demonstrated by identifying SLPI mRNA transcripts in bronchial epithelial cells freshly isolated from normals. Cell lines derived from mucosal surfaces (HS-24 bronchial squamous cell carcinoma, HeLa cervical carcinoma) actively transcribe the SLPI gene and contain SLPI mRNA transcripts, while lung fibroblasts demonstrate no evidence of SLPI gene expression. SLPI mRNA transcripts appear to be relatively stable, with mRNA levels only mildly affected by inhibition of RNA synthesis. Chromatin DNA of HS-24 cells demonstrates two DNase I hypersensitivity sites within the 5' flanking region of exon I of the SLPI gene, whereas fibroblast chromatin has no DNase I accessible sites in the same region. Further analysis of the 5' flanking region demonstrated two contiguous transcription start sites, CAAT and TATA boxes, and several potential regions of known DNA binding proteins. Overall, the SLPI gene

appears to be a relatively nonpolymorphic, stable gene that is constitutively expressed at specific tissue sites, but has the potential to be modulated at both the transcriptional and posttranscriptional levels.

L20 ANSWER 31 OF 37 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 1991-07457 BIOTECHDS
TITLE: Adeno virus-mediated transfer of a recombinant alpha-1-antitrypsin gene to the lung epithelium in vivo; gene cloning in cell culture; potential application in gene therapy
AUTHOR: Rosenfeld M A; Siegfried W; **Yoshimura K**; Yoneyama K; Fukayama M; *Crystal R G
CORPORATE SOURCE: Transgene
LOCATION: Pulmonary Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Science; (1991) 252, 5004, 431-34
CODEN: SCIEAS
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The respiratory epithelium is a potential site for somatic gene therapy for the common hereditary disorders alpha-1-antitrypsin (a1AT) deficiency and cystic fibrosis. A replication-deficient adeno virus vector containing an adeno virus major late promoter and a human recombinant a1AT gene was constructed, and was used to infect epithelium cells of the cotton rat respiratory tract in vitro and in vivo. Freshly isolated tracheobronchial epithelial cells infected with the recombinant virus contained human a1AT mRNA transcripts, and produced and secreted human a1AT. After in vivo intratracheal administration of the recombinant virus, human a1AT mRNA was observed in the respiratory epithelium, human a1AT was produced and secreted by lung tissue, and human a1AT was detected in epithelial lining fluid for at least 1 wk. These results show that the use of safe adeno virus vectors has promise for human gene therapy of a1AT deficiency and possibly cystic fibrosis. (40 ref)

L20 ANSWER 32 OF 37 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 89008342 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2902087
TITLE: Structure of the human neutrophil elastase gene.
AUTHOR: Takahashi H; Nukiwa T; **Yoshimura K**; Quick C D; States D J; Holmes M D; Whang-Peng J; Knutsen T; Crystal R G
CORPORATE SOURCE: Pulmonary Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20892.
SOURCE: Journal of biological chemistry, (1988 Oct 15) 263 (29) 14739-47.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-J04032; GENBANK-M20199; GENBANK-M20200; GENBANK-M20201; GENBANK-M20202; GENBANK-M20203
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 20000303
Entered Medline: 19881110
AB The gene for human neutrophil elastase (NE), a powerful serine **protease** carried by blood neutrophils and capable of destroying most connective tissue proteins, was cloned from a genomic DNA library of a normal individual. The NE gene consists of 5 exons and 4 introns included in a single copy 4-kilobase segment of chromosome 11 at q14. The coding exons of the NE gene predict a primary translation product of 267 residues including a 29-residue N-terminal precursor peptide and a

20-residue C-terminal precursor peptide. Analysis of the N-terminal peptide sequence suggests it contains a 27-residue "pre" signal peptide followed by a "proN" dipeptide, similar to that of other blood cell lysosomal **proteases**. The sequences for the mature 218-residue NE protein are included in exons II-V. The 5'-flanking region of the gene includes typical TATA, CAAT, and GC sequences within 61 base pairs (bp) of the cap site. The sequence 1.5 kilobases 5' to exon I contains several interesting repetitive sequences including six tandem repeats of unique 52- or 53-bp sequences. The 5'-flanking region also contains a 19-bp segment with 90% homology to a segment of the 5'-flanking region of the human myeloperoxidase (MPO) gene, a gene also expressed in bone marrow precursor cells and a protein stored in the same neutrophil granules as NE. In addition, like the MPO gene, the NE 5'-flanking region has several regions with greater than or equal to 75% homology to sequences 5' to c-myc, but there is no overlap between the NE-c-myc and MPO-c-myc homologous sequences.

L20 ANSWER 33 OF 37 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 86286592 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3016665
TITLE: Cloning and sequencing of Serratia **protease** gene.
AUTHOR: Nakahama K; **Yoshimura K**; Marumoto R; Kikuchi M; Lee I S; Hase T; Matsubara H
SOURCE: Nucleic acids research, (1986 Jul 25) 14 (14) 5843-55. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X04127
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19860917

AB The gene encoding an extracellular metalloproteinase from Serratia sp. E-15 has been cloned, and its complete nucleotide sequence determined. The amino acid sequence deduced from the nucleotide sequence reveals that the mature protein of the Serratia **protease** consists of 470 amino acids with a molecular weight of 50,632. The G+C content of the coding region for the mature protein is 58%; this high G+C content is due to a marked preference for G+C bases at the third position of the codons. The gene codes for a short pro-peptide preceding the mature protein. The Serratia **protease** gene was expressed in Escherichia coli and Serratia marcescens; the former produced the Serratia **protease** in the cells and the latter in the culture medium. Three zinc ligands and an active site of the Serratia **protease** were predicted by comparing the structure of the enzyme with those of thermolysin and Bacillus subtilis neutral **protease**.

L20 ANSWER 34 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 86:430008 SCISEARCH
THE GENUINE ARTICLE: D3426
TITLE: CLONING AND SEQUENCING OF SERRATIA **PROTEASE** GENE
AUTHOR: NAKAHAMA K (Reprint); **YOSHIMURA K**; MARUMOTO R; KIKUCHI M; LEE I S; HASE T; MATSUBARA H
CORPORATE SOURCE: TAKEDA CHEM IND LTD, DIV CENT RES, BIOTECHNOL LABS, YODOGAWA KU, OSAKA 532, JAPAN (Reprint); OSAKA UNIV, FAC SCI, DEPT BIOL, TOYONAKA, OSAKA 560, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: NUCLEIC ACIDS RESEARCH, (1986) Vol. 14, No. 14, pp. 5843-5855.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH

REFERENCE COUNT: 33

L20 ANSWER 35 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 18
ACCESSION NUMBER: 86094908 EMBASE
DOCUMENT NUMBER: 1986094908
TITLE: Bacillus subtilis secretes a foreign protein by the signal sequence of Bacillus amyloliquefaciens neutral **protease**.
AUTHOR: **Yoshimura K.**; Miyazaki T.; Nakahama K.; Kikuchi M.
CORPORATE SOURCE: Biotechnology Laboratories, Central Research Division, Takeda Chemical Industries, Yodogawa-ku, Osaka 532, Japan
SOURCE: Applied Microbiology and Biotechnology, (1986) 23/3-4 (250-256).
CODEN: AMBIDG
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
LANGUAGE: English

L20 ANSWER 36 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 86:82472 SCISEARCH
THE GENUINE ARTICLE: AZC78
TITLE: BACILLUS-SUBTILIS SECRETES A FOREIGN PROTEIN BY THE SIGNAL SEQUENCE OF BACILLUS-AMYLOLIQUEFACIENS NEUTRAL **PROTEASE**
AUTHOR: **YOSHIMURA K (Reprint)**; MIYAZAKI T; NAKAHAMA K; KIKUCHI M
CORPORATE SOURCE: TAKEDA CHEM IND LTD, DIV CENT RES, BIOTECHNOL LABS, 17-85 JUSOHONMACHI 2-CHOME, YODOGAWA KU, OSAKA 532, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: APPLIED MICROBIOLOGY AND BIOTECHNOLOGY, (1986) Vol. 23, No. 3-4, pp. 250-256.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 38

L20 ANSWER 37 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1985:433877 BIOSIS
DOCUMENT NUMBER: PREV198580103869; BA80:103869
TITLE: CLONING AND PARTIAL NUCLEOTIDE SEQUENCE OF NEUTRAL **PROTEASE** GENE FROM BACILLUS-AMYLOLIQUEFACIENS.
AUTHOR(S): **YOSHIMURA K** [Reprint author]; MIYAZAKI T; NAKAHAMA K; KIKUCHI M
CORPORATE SOURCE: CENTRAL RESEARCH DIV, TAKEDA CHEMICAL INDUSTRIES, LTD, 17-85 JUSOHONMACHI, 2-CHOME, YODOGAWA-KU, OSAKA 532, JAPAN
SOURCE: Journal of Takeda Research Laboratories, (1985) Vol. 44, No. 1-2, pp. 42-50.
CODEN: TAKHAA. ISSN: 0371-5167.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
AB The gene coding for neutral **protease** of B. amyloliquefaciens was cloned in a neutral **protease** deficent mutant of B. subtilis and partially sequenced. The gene product was isolated from a culture supernatant of the recombinant and its NH2-terminal amino acid sequence was determined. Based on these results, an open reading frame with a signal peptide, a pro-peptide and the mature enzyme was deterined. In addition, putative promoters, a ribosome binding site and a transcription termination region are presented in the nucleotide sequence.

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=> d his

     (FILE 'HOME' ENTERED AT 14:43:00 ON 07 JUL 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:43:25 ON 07 JUL 2004
L1         18018 S "ADAM"
L2             2 S "A DISTINTEGRIN AND METALLOPROTEASE"
L3             2 DUP REM L2 (0 DUPLICATES REMOVED)
L4        416281 S PROTEASE OR DINITEGRIN
L5        420704 S PROTEASE OR DISINTEGRIN
L6          1933 S L1 AND L5
L7           990 S HUMAN AND L6
L8       6594644 S CLON? OR EXPRESS? OR RECOMBINANT
L9           751 S L7 AND L8
L10            0 S PROTEOIGLYCAN
L11        91811 S PROTEOGLYCAN
L12           28 S L9 AND L11
L13           14 DUP REM L12 (14 DUPLICATES REMOVED)
                 E YOSHIMURA K/AU
L14         3665 S E3
                 E HIKICHI Y/AU
L15          273 S E3
                 E NISHIMURA A/AU
L16         1666 S E3
L17         5594 S L14 OR L15 OR L16
L18            0 S L1 AND L17
L19           82 S L5 AND L17
L20           37 DUP REM L19 (45 DUPLICATES REMOVED)
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	Issue Date	Pages	Document ID	Title
1	20040513	115	US 20040091962 A1	Proteases
2	20040429	67	US 20040081971 A1	Protein modification and maintenance molecules
3	20040429	95	US 20040081961 A1	Proteases
4	20040422	108	US 20040077048 A1	Protein modification and maintenance molecules
5	20040318	105	US 20040053269 A1	Proteases
6	20040318	243	US 20040053248 A1	Novel nucleic acids and polypeptides
7	20040304	207	US 20040043021 A1	Nucleotide and amino acid sequences relating to respiratory diseases and obesity
8	20040212	106	US 20040029249 A1	Proteases

	Issue Date	Pages	Document ID	Title
9	20040205	118	US 20040023243 A1	Proteases
10	20040122	24	US 20040014636 A1	Pharmaceutical compositions comprising a modulator of adamts-1
11	20040108	245	US 20040006016 A1	Novel 27875, 22025 ,27420, 17906, 16319, 55092 and 10218 molecules and uses therefor
12	20040108	345	US 20040005563 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer
13	20031218	121	US 20030232349 A1	Proteases
14	20031204	320	US 20030225009 A1	28 human secreted proteins
15	20030904	36	US 20030166562 A1	Treatment for asthma or allergies
16	20030814	278	US 20030154032 A1	Methods and compositions for diagnosing and treating rheumatoid arthritis
17	20030703	81	US 20030124706 A1	Proteases

	Issue Date	Pages	Document ID	Title
18	20030703	64	US 20030124579 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer
19	20030417	111	US 20030073622 A1	Novel proteins and nucleic acids encoding same
20	20030220	281	US 20030037350 A1	Novel nucleic acid sequences encoding a human ubiquitin protease, lipase, dynamin, short chain dehydrogenase, and ADAM-TS metalloprotease and uses therefor
21	20030123	71	US 20030017572 A1	56294 and 56629, novel human metalloproteases and uses thereof
22	20021219		US 20020192748 A1	Novel polynucleotides and polypeptides encoded thereby
23	20021031		US 20020161214 A1	Novel human proteases and polynucleotides encoding the same
24	20020919		US 20020132778 A1	Modulating angiogenesis
25	20020808		US 20020107361 A1	Novel metalloproteases having thrombospondin domains and nucleic acid compositions encoding the same
26	20020725		US 20020099004 A1	Inhibition of invasive remodelling

	Issue Date	Pages	Document ID	Title
27	20020620		US 20020076778 A1	33428, a novel human metalloprotease family member and uses thereof
28	20020613		US 20020072490 A1	33428, a novel human metalloprotease family member and uses thereof
29	20031118		US 6649589 B1	Use of certain drugs for treating nerve root injury
30	20020820		US 6436629 B1	Modulating angiogenesis
31	19990713		US 5922546 A	Human disintegrin metalloprotease KUZ gene

	Issue Date	Pages	Document ID	Title
1	20040513	115	US 20040091962 A1	Proteases
2	20040429	67	US 20040081971 A1	Protein modification and maintenance molecules
3	20040429	95	US 20040081961 A1	Proteases
4	20040422	108	US 20040077048 A1	Protein modification and maintenance molecules
5	20040318	105	US 20040053269 A1	Proteases
6	20040212	106	US 20040029249 A1	Proteases
7	20040205	118	US 20040023243 A1	Proteases
8	20031218	121	US 20030232349 A1	Proteases

	Issue Date	Pages	Document ID	Title
9	20030814	278	US 20030154032 A1	Methods and compositions for diagnosing and treating rheumatoid arthritis
10	20030703	81	US 20030124706 A1	Proteases
11	20030703	64	US 20030124579 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer
12	20020808	48	US 20020107361 A1	Novel metalloproteases having thrombospondin domains and nucleic acid compositions encoding the same

	Issue Date	Pages	Document ID	Title
1	20040304	32	US 20040043387 A1	Nucleic acid molecules and polypeptides related to h-ADAM7
2	20040304	207	US 20040043021 A1	Nucleotide and amino acid sequences relating to respiratory diseases and obesity
3	20040205	485	US 20040023215 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
4	20040108	245	US 20040006016 A1	Novel 27875, 22025 ,27420, 17906, 16319, 55092 and 10218 molecules and uses therefor
5	20040101	441	US 20040002470 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
6	20030724	417	US 20030138925 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
7	20030417	111	US 20030073622 A1	Novel proteins and nucleic acids encoding same
8	20030123	71	US 20030017572 A1	56294 and 56629, novel human metalloproteases and uses thereof

	Issue Date	Pages	Document ID	Title
9	20021219	100	US 20020192748 A1	Novel polynucleotides and polypeptides encoded thereby
10	20020829	71	US 20020119555 A1	53014, a human metalloprotease family member and uses therefor
11	20020620	55	US 20020076778 A1	33428, a novel human metalloprotease family member and uses thereof
12	20020613	67	US 20020072490 A1	33428, a novel human metalloprotease family member and uses thereof

	Issue Date	Pages	Document ID	Title
1	20040624	483	US 20040121396 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
2	20040624	217	US 20040121349 A1	Novel 27877, 18080, 14081, 32140, 50352, 16658, 14223, 16002, 50566, 65552 and 65577 molecules and uses therefor
3	20040610	170	US 20040110938 A1	Proteins, genes and their use for diagnosis and treatment of schizophrenia
4	20040506	68	US 20040086494 A1	Immune privileged cells for delivery of proteins and peptides
5	20040429	44	US 20040082018 A1	Methods for using osteocalcin
6	20040429	51	US 20040081970 A1	Calcium-sensing receptor 2 (CaR2) and methods for using
7	20040429	44	US 20040081658 A1	Long peptides of 22-45 amino acid residues that induce and/or enhance antigen specific immune responses
8	20040318	132	US 20040054158 A1	GL50 molecules and uses therefor

	Issue Date	Pages	Document ID	Title
9	20040318	50	US 20040053841 A1	Inhibitors of the interaction between HMGB polypeptides and toll-like receptor 2 as anti-inflammatory agents
10	20040318	44	US 20040053830 A1	BCMP84 protein, compositions, diagnostic and therapeutic uses thereof
11	20040318	107	US 20040053309 A1	Proteins, genes and their use for diagnosis and treatment of kidney response
12	20040304	52	US 20040043425 A1	Proteins, genes and their use for diagnosis and treatment of chronic asthma
13	20040304	32	US 20040043387 A1	Nucleic acid molecules and polypeptides related to h-ADAM7
14	20040304	207	US 20040043021 A1	Nucleotide and amino acid sequences relating to respiratory diseases and obesity
15	20040226	61	US 20040038338 A1	Influence of LRP cytoplasmic domain on Abeta production
16	20040205	485	US 20040023215 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
17	20040205	73	US 20040023207 A1	Assays for drug discovery based on microcompetition with a foreign polynucleotide

	Issue Date	Pages	Document ID	Title
18	20040205	72	US 20040023206 A1	Methods for chronic disease diagnosis based on microcompetition with a foreign polynucleotide
19	20040205	70	US 20040022794 A1	Nucleic acid molecules, polypeptides and uses therefor, including diagnosis and treatment of Alzheimer's disease
20	20040205	63	US 20040022764 A1	Inhibition of microcompetition with a foreign polynucleotide as treatment of chronic disease
21	20040129	107	US 20040018533 A1	Diagnosing predisposition to fat deposition and therapeutic methods for reducing fat deposition and treatment of associated conditions
22	20040129	68	US 20040018499 A1	Extracellular messengers
23	20040122	37	US 20040014156 A1	Monoclonal antibody for analysis and clearance of polyethylene glycol and polyethylene glycol-modified molecules

	Issue Date	Pages	Document ID	Title
24	20040115	260	US 20040009553 A1	Novel 27411, 23413, 22438, 23553, 25278, 26212, NARC SC1, NARC 10A, NARC 1, NARC 12, NARC 13, NARC17, NARC 25, NARC 3, NARC 4, NARC 7, NARC 8, NARC 11, NARC 14A, NARC 15, NARC 16, NARC 19, NARC 20, NARC 26, NARC 27, NARC 28, NARC 30, NARC 5, NARC 6, NARC 9, NARC 10C, NARC 8B, NARC 9, NARC2A, NARC 16B, NARC 1C, NARC1A, NARC 25, 86604 and 32222 molecules and uses therefor
25	20040108	245	US 20040006016 A1	Novel 27875, 22025 ,27420, 17906, 16319, 55092 and 10218 molecules and uses therefor
26	20040101	441	US 20040002470 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
27	20040101	144	US 20040001826 A1	Glycoprotein VI and uses thereof
28	20031218	144	US 20030233670 A1	Gene sequences and uses thereof in plants
29	20031211	75	US 20030228583 A1	Biomarkers of liver response
30	20031204	38	US 20030225027 A1	Telomerase reverse transcriptase fragments and uses thereof

	Issue Date	Pages	Document ID	Title
31	20031204	103	US 20030224451 A1	Novel protein related to melanoma-inhibiting protein and uses thereof
32	20031120		US 20030215805 A1	Novel genes, compositions, kits, and methods for identification, assessment prevention, and therapy of breast cancer
33	20031113		US 20030212256 A1	Proteins and nucleic acids encoding same
34	20031009		US 20030190709 A1	Pablo, a polypeptide that interacts with Bcl-xL, and uses related thereto
35	20031009		US 20030190615 A1	DPI-6, a putative therapeutic target and biomarker in neuropsychiatric and neurological disorders
36	20030925		US 20030180888 A1	CD2000 and CD2001 molecules, and uses thereof
37	20030918		US 20030175890 A1	FAIL molecules and uses thereof
38	20030911		US 20030170621 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
39	20030904		US 20030166502 A1	Differential regulation of T cell survival and proliferation

	Issue Date	Pages	Document ID	Title
40	20030821	80	US 20030157082 A1	Methods and compositions for treating cancer using 140, 1470, 1686, 2089, 2427, 3702, 5891, 6428, 7181, 7660, 25641, 69583, 49863, 8897, 1682, 17667, 9235, 3703, 14171, 10359, 1660, 1450, 18894, 2088, 32427, 2160, 9252, 9389, 1642, 85269, 10297, 1584, 9525, 14124, 4469, 8990, 2100, 9288, 64698, 10480,20893, 33230,1586, 9943, 16334, 68862, 9011, 14031, 6178, 21225, 1420, 32236, 2099, 2150, 26583, 2784, 8941, 9811, 27444, 50566 or 66428 molecules
41	20030814		US 20030153018 A1	Methods and compositions for treating cancer using 2192, 2193, 6568, 8895, 9138, 9217, 9609, 9857, 9882, 10025, 20657, 21163, 25848, 25968, 32603, 32670, 33794, 54476 and 94710
42	20030814		US 20030152935 A1	Proteins, genes and their use for diagnosis and treatment of breast cancer
43	20030807		US 20030148410 A1	Novel genes, compositions, kits, and methods for identification, assessment, prevention, and therapy of colon cancer
44	20030724		US 20030139544 A1	Catalyst system for the polymerization of alkenes to polyolefins

	Issue Date	Pages	Document ID	Title
45	20030724	417	US 20030138925 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
46	20030605		US 20030104447 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic and other uses
47	20030605	168	US 20030104358 A1	Diagnosis methods based on microcompetition for a limiting GABP complex
48	20030515		US 20030092614 A1	ADPI-41, a novel protein isolated from brain tissue homogenate and uses therefor
49	20030515		US 20030092601 A1	Microcompetition and human disease
50	20030515		US 20030092197 A1	Proteins, genes and their use for diagnosis and treatment of cardiac response
51	20030501		US 20030083254 A1	Substances
52	20030417	111	US 20030073622 A1	Novel proteins and nucleic acids encoding same
53	20030410		US 20030069199 A1	Treatment methods based on microcompetition for a limiting GABP complex
54	20030410		US 20030068616 A1	Drug discovery assays based on microcompetition for a limiting GABP complex

	Issue Date	Pages	Document ID	Title
55	20030403		US 20030064419 A1	Proteins, genes and their use for diagnosis and treatment of breast cancer
56	20030403		US 20030064411 A1	Nucleic acid molecules, polypeptides and uses therefor, including diagnosis and treatment of Alzheimer's disease
57	20030327		US 20030060459 A1	Diamines as modulators of chemokine receptor activity
58	20030320		US 20030054332 A1	Markers for evaluating estrogenic activity
59	20030313		US 20030049640 A1	Proteins, genes and their use for diagnosis and treatment of vascular response
60	20030306		US 20030044946 A1	Genes, mutations, and drugs that increase cellular resistance to damage and extend longevity in organisms from yeast to humans
61	20030213		US 20030032773 A1	Proteins, genes and their use for diagnosis and treatment of bipolar affective disorder (BAD) and unipolar depression

	Issue Date	Pages	Document ID	Title
62	20030213		US 20030032200 A1	Proteins, genes and their use for diagnosis and treatment of bipolar affective disorder (BAD) and unipolar depression
63	20030206		US 20030027998 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
64	20030206		US 20030027354 A1	Device for the analysis of chemical or biochemical specimens, comparative analysis, and associated analysis process
65	20030130		US 20030022279 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
66	20030123	71	US 20030017572 A1	56294 and 56629, novel human metalloproteases and uses thereof
67	20030123		US 20030017456 A1	Diagnosis and treatment and related preparations
68	20021219	100	US 20020192748 A1	Novel polynucleotides and polypeptides encoded thereby
69	20021107		US 20020164668 A1	Nucleic acid molecules, polypeptides and uses therefor, including diagnosis and treatment of alzheimer's disease
70	20021003		US 20020142303 A1	Proteins, genes and their use for diagnosis and treatment of Schizophrenia

	Issue Date	Pages	Document ID	Title
71	20020926		US 20020137049 A1	Pablo, a polypeptide that interacts with Bcl-xL, and uses related thereto
72	20020919		US 20020132297 A1	Novel molecules of the herpesvirus-entry-mediator-related protein family and use thereof
73	20020829	71	US 20020119555 A1	53014, a human metalloprotease family member and uses therefor
74	20020815		US 20020111303 A1	Diagnostic and therapeutic methods
75	20020801		US 20020103360 A1	Novel protein related to melanoma-inhibiting protein and uses thereof
76	20020620	55	US 20020076778 A1	33428, a novel human metalloprotease family member and uses thereof
77	20020613	67	US 20020072490 A1	33428, a novel human metalloprotease family member and uses thereof
78	20020606		US 20020068696 A1	Trade molecules and uses related thereto
79	20020509		US 20020055139 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
80	20020502		US 20020051982 A1	Novel BLR molecules affecting antibiotic susceptibility
81	20020502		US 20020051181 A1	Information processing apparatus and method, information processing system and medium

	Issue Date	Pages	Document ID	Title
82	20020307		US 20020028508 A1	Novel genes encoding proteins having prognostic, diagnostic, preventive , therapeutic and other uses
83	20020207		US 20020016289 A1	METHODS FOR TREATMENT AND PREVENTION OF HELICOBACTER PYLORI INFECTION USING LACTOFERRIN
84	20011011	40	US 20010028881 A1	Monoclonal antibody for analysis and clearance of polyethylene glycol and polyethylene glycol-modified molecules
85	20040622		US 6754108 B2	DRAM cells with repressed floating gate memory, low tunnel barrier interpoly insulators
86	20040525		US 6741529 B1	Method and apparatus for moving carriage assembly from initial position to target position and optical disc system including same
87	20040406		US 6716974 B1	Therapeutic and diagnostic methods and compositions based on jagged/notch proteins and nucleic acids
88	20040302		US 6699667 B2	Molecular wire injection sensors

	Issue Date	Pages	Document ID	Title
89	20040210		US D486434 S	Ergonomic clutch/brake handle
90	20040127		US 6682485 B2	Noninvasive apparatus and method for the determination of cardiac valve function
91	20040120		US 6680189 B1	Protein and DNA thereof
92	20031230		US 6671253 B1	Method and system for providing peer redundancy to asynchronous transfer mode emulated local-area networks
93	20031216		US 6664068 B2	Pablo, a polypeptide that interacts with Bcl-xL, and uses related thereto
94	20030930		US D480028 S	Ergonomic clutch/brake handle
95	20030909	34	US 6617118 B2	Monoclonal antibody for analysis and clearance of polyethylene glycol and polyethylene glycol-modified molecules
96	20030722	40	US 6596849 B1	Monoclonal-antibody for analysis and clearance of polyethylene glycol and polyethylene glycol-modified molecules
97	20030617		US 6580881 B2	Method of detecting waste toner in a container of an image forming apparatus
98	20030527		US 6568594 B1	Optical scanning device
99	20030513		US 6560928 B2	System for assembling two components of a window regulator activation device on a support

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100	20030218		US 6521749 B1	GL50 nucleic acids and uses therefor
101	20030218		US 6521420 B1	Hypertension associated transcription factors and uses therefor
102	20030211		US 6518305 B1	Five-membered carbocyclic and heterocyclic inhibitors of neuraminidases
103	20030107		US 6503498 B1	Apolipoprotein A-1 adenovirus vector compositions and methods
104	20030107		US 6503380 B1	Physical vapor target constructions
105	20021029		US 6471613 B1	Transmission with variable line pressure
106	20021015		US 6466368 B1	Rear projection screen with reduced speckle
107	20021008		US 6463397 B1	Environmental monitoring and control system for a ventilated cage and rack system
108	20020924		US 6457164 B1	Hetergeneous method for determining module placement in FPGAs
109	20020813		US 6434748 B1	Method and apparatus for providing VCR-like "trick mode" functions for viewing distributed video data

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110	20020813		US 6434087 B1	Optical disc system and method for controlling bias coil and light source to process information on a storage medium
111	20020806		US 6430732 B1	Method for structured layout in a hardware description language
112	20020730		US 6426114 B1	Sol-gel calcium phosphate ceramic coatings and method of making same
113	20020709		US 6418097 B1	Analog to digital converter assembly for normalizing servo error signals and multiplexing reference voltage inputs and digital outputs and improved optical drive system including same
114	20020618		US 6408422 B1	Method for remapping logic modules to resources of a programmable gate array
115	20020618		US 6406884 B1	Secreted proteins and uses thereof
116	20020507		US 6383779 B1	Glycoprotein VI and uses thereof
117	20020430		US 6379303 B1	Noninvasive apparatus and method for the determination of cardiac valve function
118	20020326		US 6362270 B1	Thermoplastic compositions for durable goods applications

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119	20020319		US 6359194 B1	Compositions and methods for the treatment and diagnosis of cardiovascular disease
120	20020205		US 6345055 B1	Method and system for providing interoperability between network clients having different versions of local-area network emulation user network interface within an asynchronous transfer mode emulated local-area network
121	20011225		US 6332835 B1	Polishing apparatus with transfer arm for moving polished object without drying it
122	20011218		US 6331467 B1	Method of manufacturing a trench gate field effect semiconductor device

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123	20011204		US 6326215 B1	Molecular wire injection sensors
124	20011113		US 6317391 B1	Optical disc system having current monitoring circuit with improved bias coil assembly and controller for laser driver and method for operating same
125	20010925		US 6294111 B1	Electrochromic inks
126	20010918		US 6292925 B1	Context-sensitive self implementing modules
127	20010904		US 6285155 B1	Pseudo half-step motor drive method and apparatus

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128	20010821		US 6278665 B1	Optical disc system including current monitoring circuit assembly having controller with improved optics module and laser driver and method for operating same
129	20010724		US 6266306 B1	Analog to digital converter and assembly for use in optical drive system to normalize servo error signals and multiplex reference voltage inputs and digital outputs
130	20010710		US 6260182 B1	Method for specifying routing in a logic module by direct module communication
131	20010612		US 6245527 B1	Nucleic acid molecules encoding glycoprotein VI and recombinant uses thereof
132	20010605		US 6243851 B1	Heterogeneous method for determining module placement in FPGAs
133	20010605		US 6243336 B1	Optical disc system having servo motor and servo error detection assembly operated relative to monitored quad sum signal and focus capture method for use in same
134	20010522		US 6237129 B1	Method for constraining circuit element positions in structured layouts

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135	20010522		US 6236625 B1	Optical disc system having current monitoring circuit with controller for laser driver and method for operating same
136	20010320		US 6204248 B1	Pharmaceutical preparations of glutathione and methods of administration thereof
137	20001121		US 6149595 A	Noninvasive apparatus and method for the determination of cardiac valve function
138	20000919		US 6122232 A	Isolation apparatus for use in disc drive system to mitigate effects of undesired mechanical forces and disc drive system including same
139	20000711		US 6087644 A	Focus capture for optical disc system including detection of quad sum signal to close focus
140	20000509		US 6060327 A	Molecular wire injection sensors
141	20000307		US 6034364 A	Optical disc system including focus capture assembly with focus error signal circuit and method for operating same

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143	20000208		US 6022293 A	Electronic control of transmission line pressure
144	19991228		US 6006748 A	Vent valve apparatus
145	19991207		US 5996467 A	Polymer-metal coatings for swashplate compressors
146	19990810		US 5934902 A	Oral cleansing device
147	19990720		US 5926205 A	Method and apparatus for encoding and formatting data representing a video program to provide multiple overlapping presentations of the video program
148	19990518		US 5905377 A	Method and apparatus for correcting gradient system and static magnetic field in magnetic resonance imaging
149	19980811		US 5793059 A	Static random access memory cell and method of fabricating the same
150	19980811		US 5792771 A	Quinazoline compounds and compositions thereof for the treatment of disease

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154	19971118		US 5688511 A	Cellular protein TDP-43 and regulation of HIV-1 gene expression
155	19970610		US 5637721 A	Process for the preparation of cephem prodrug esters
156	19970401		US 5617486 A	Continuous reference adaptation in a pattern recognition system
157	19970325		US 5614623 A	Diastereomers of 1-(isopropoxycarbonyloxy)ethyl 3-cephem-4-carboxylate and processes for their preparation
158	19970114		US 5594133 A	Crystalline acid addition salts of diastereomerically pure 1-(2,2-dimethylpropinonyloxy)-ethyl-3-cephem-4-carboxylate
159	19961231		US 5589594 A	Process for the preparation of cephem prodrug esters

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160	19960917		US 5556850 A	Crystalline acid addition salts of diastereomerically pure 1-(2,2-dimethyl-propionyloxy)-ethyl-3-cephem-4-carboxylate
161	19960827		US 5550232 A	Diastereomers of 1-(isopropoxycarbonyloxy) ethyl 3-cephem 4-carboxylate
162	19960319		US 5499629 A	Slice profile stabilization for segmented k-space magnetic resonance imaging
163	19951024		US 5461043 A	Diastereomers of 1-(isopropoxycarbonyloxy)ethyl 3-cephem-4-carboxylate
164	19950425		US 5410042 A	Process for the cleavage of cephalosporin prodrug esters to 7-amino-3-methoxymethyl ceph-3-em-4-carboxylic acid
165	19950425		US 5409918 A	Crystalline cephem acid addition salts and process for their preparation
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169	19940419		US 5303714 A	Guidewire for crossing occlusions in blood vessels
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172	19910910		US 5047013 A	Varicose vein probe with hollow curved spiral tip
173	19910723		US 5034778 A	Background cleaning system for liquid developer imaging apparatus
174	19890117		US 4799191 A	Memory saving electronic dictionary system for spell checking based on noun suffix
175	19890117		US 4799188 A	Electronic dictionary system having improved memory efficiency for storage of common suffix words
176	19890103		US 4795725 A	Method for the manufacture of refractory bricks containing CaO
177	19881122		US 4787059 A	System for effective spell check in word processing with relocated starting location
178	19880503		US 4742481 A	Electronic dictionary having means for linking two or more different groups of vocabulary entries in a closed loop
179	19870929		US 4697107 A	Four-state I/O control circuit
180	19850507		US 4515891 A	Process for the production of disaccharide-tripeptide and disaccharide-tetrapeptide

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183	19810317		US 4256735 A	Immunologically active dipeptidyl saccharides and methods of preparation

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1	L1	13994	"ADAM"
2	L2	54881	protease$2
3	L3	3142	metalloprotease$2
4	L4	259	l1 same l3
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6	L6	157	l4 same l5
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8	L8	31	l6 same l7
9	L9	5115	proteoglycan
10	L10	12	l8 same l9
11	L11	24730	YOSHIMURA HIKICHI NISHIMURA
12	L12	12	l6 and l11
13	L13	183	l1 and l11